Medicinrådet

Bilag til Medicinrådets anbefaling vedr. atezolizumab til adjuverende behandling af ikke-småcellet lungekræft

Voksne patienter efter komplet resektion og adjuverende platinbaseret kemoterapi med høj risiko for tilbagefald og med PD-L1-ekspression ≥ 50 %

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. atezolizumab til adjuverende behandling af ikke-småcellet lungekræft
2. Ansøgers endelige ansøgning vedr. atezolizumab til adjuverende behandling af ikke-småcellet lungekræft

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

20.02.2023

DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.03.2023
Leverandør	Roche
Lægemiddel	Tecentriq (atezolizumab)
Ansøgt indikation	Tecentriq (atezolizumab) til adjuverende behandling af ikke-småcellet lungekræft
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende pris på Tecentriq:

Tabel 1: aftalepris Tecentriq

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Rabatprocent ift. AIP
Tecentriq	840 mg	1 stk.	20.722	[redacted]	[redacted]
Tecentriq	1200 mg	1 stk.	29.603	[redacted]	[redacted]

Aftaleforhold

Amgros har en aftale på Tecentriq og lægemidlet er en del af et fleksibelt udbud sammen med Opdivo (nivolumab) og Keytruda (pembolizumab). Aftalen udløber 31.12.2023.

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence indenfor denne indikation.
[redacted]

Leverandøren planlægger at markedsføre en SC formulering i løbet af 2023. Der er ligeledes planlagt at markedsføre SC formuleringer fra både Opdivo (nivolumab) og Keytruda (pembolizumab), tidsplanen for dette er dog endnu uvis.

Status fra andre lande

Land	Status	Link
Norge	Under vurdering	https://nyemetoder.no/metoder/atezolizumab-tecentriq-indikasjon-xx
England	Anbefalet	https://www.nice.org.uk/guidance/ta823/chapter/1-Recommendations

Konklusion

Amgros vurderer, at leverandøren på nuværende tidspunkt **ikke** kan give en bedre pris på denne indikation.

Application for the assessment of atezolizumab (Tecentriq) as adjuvant treatment for patients with stage II to IIIA NSCLC and PD-L1 expression ≥ 50% of TC and who do not have EGFR mutant or ALK-positive NSCLC

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1. Basic information

Contact information	
Name	**Christian Graves Beck**
Title	Strategic Market Access Partner
Phone number	+45 23 44 20 83
E-mail	christian_graves.beck@roche.com
Name	**Pia Møllgaard Mikkelsen**
Title	Scientific Partner
Phone number	+45 24886085
E-mail	pia.mollgaard@roche.com
Name	**Ditte Marie Clugston**
Title	Medical Writer
Phone number	+45 42 14 29 44
E-mail	ditte_marie.clugston@roche.com

Overview of the pharmaceutical	
Proprietary name	Tecentriq
Generic name	Atezolizumab
Marketing authorization holder in Denmark	Roche A/S
ATC code	L01FF05
Pharmacotherapeutic group	Monoclonal antibody
Active substance	Atezolizumab
Pharmaceutical form	Concentrate for solution for infusion
Mechanism of action	Atezolizumab inhibits immune checkpoint programmed death ligand 1 (PD-L1)
Dosage regimen	840 mg administered intravenously every 2nd week or 1200 mg administered intravenously every 3rd week or 1680 mg administered intravenously every 4th week
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with non-small cell lung cancer (NSCLC) with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC

Overview of the pharmaceutical	
Other approved therapeutic indications	**Urothelial carcinoma** Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy, or who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%. **Metastatic non-small cell lung cancer** Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving Tecentriq. Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies. Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC. Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with metastatic NSCLC, whose tumours have a PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating immuncells (IC) and who do not have EGFR mutant or ALK-positive NSCLC. **Small cell lung cancer** Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). **Triple-negative breast cancer** Tecentriq in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease. **Hepatocellular carcinoma** Tecentriq in combination with bevacizumab is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy.
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	Conc. for solution for infusion, 840 mg 1 vial Conc. for solution for infusion, 1200 mg 1 vial
Orphan drug designation	No

2. Abbreviations

1L	First-line
1LM	First-line metastatic recurrence
2L	Second-line
2LM	Second-line metastatic recurrence
3L	Third-line
4L	Fourth-line
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
AR	Assessment report
ATZ	Atezolizumab
BSC	Best supportive care
CCOD	Clinical cut-off date
CD	Cluster of differentiation
CE	Cost-effectiveness
CI	Confidence interval
CRT	Chemoradiotherapy
CIT	Cancer immunotherapy
CT	Computed tomography
ctDNA	Circulating tumour DNA
DFS	Disease-free survival
DKK	Danish krones
DLCG	Danish Lung Cancer Group
DLCR	Danish Lung Cancer Registry
DMC	Danish Medicines Council
DRG	Diagnosis related groups
DSA	Deterministic sensitivity analysis
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EPAR	European public assessment report
EFS	Event-free survival
HSUV	Health state utility values
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
IV	Intravenous
Kg	Kilograms
LYs	Life years
M^2	Square meter
Mg	Milligram
MLND	Mediastinal lymph node dissection
Mo	Months

N	Number of patients
N/A	Not applicable
NE	Not estimable
NR	Not reached
NSCLC	Non-small cell lung cancer
OS	Overall survival
pCR	Pathologic complete response
PD-1	Anti-programmed death-1
PD-L1	Programmed death-ligand 1
PET	Positron emission tomography
PFS	Progressions-free survival
PLC	Pulmonary lymphangitic carcinomatosis
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
q21d	Every 21 days
QALY	Quality-adjusted life years
R	Randomisation
RT	Radiotherapy
SAE	Serious adverse event
SCLC	Small cell lung cancer
SLR	Systematic literature review
SOC	Standard of care
TAE	Therapeutic area experts
TC	Tumour cells
TPS	Tumour Proportion Score
TRAE	Treatment-related adverse event
TR-SAE	Treatment-related serious adverse event
TTOT	Time to off treatment
UICC	Union for International Cancer Control
WCLC	World Conference on Lung Cancer
WTP	Willingness to Pay

3. Tables and Figures

4. Summary

4.1 Introduction

On June 7, 2022, the European Commission (EC) approved atezolizumab (Tecentriq) as adjuvant treatment, following complete resection and platinum-based chemotherapy, for adult patients with non-small cell lung cancer (NSCLC) with a high risk of recurrence whose tumours express programmed death-ligand 1 (PD-L1) ≥50% and who do not have epidermal growth factor receptor (EGFR) mutant or anaplastic lymphoma kinase (ALK)-positive NSCLC. The recommendation is based on results from IMpower010, a randomised, multicentre, open-label, phase III study designed to investigate the efficacy and safety of adjuvant treatment with atezolizumab compared to best supportive care (BSC) in adults patients with stage IB-IIIA NSCLC following resection and adjuvant chemotherapy. This application, submitted to the Danish Medicines Council on August 10, 2022 and re-submitted on November 27, 2022, provides the basis for the assessment of atezolizumab in comparison with Danish standard of care.

Approximately 50% of patients with NSCLC have localised (stage I and II) or locally advanced (stage III) disease at the time of diagnosis. In Denmark, surgery with curative intent is the golden standard. In addition, patients with a high risk of recurrence will be offered adjuvant chemotherapy. The current standard treatment is four series of platinum doublet initiated within 6-8 weeks after surgery. Treatment results in a modest 4-5% improvement in survival vs. observation. The percentage of patients who have disease recurrence or who die after surgery over approximately 5 years of follow-up remains high, ranging from approximately 35% among patients with stage IB disease to 65% among those with stage III disease, regardless of the use of perioperative chemotherapy. Thus, there is a need to improve outcomes in early stage lung cancer.

4.2 Clinical assessment

METHODS: The clinical assessment is based on one clinical question defined by PICO, addressing the efficacy and safety of atezolizumab compared to BSC for NSCLC patients with stage II-IIIA disease following complete resection and platinum-based chemotherapy with PD-L1 expression of ≥50% of tumour cells (TC) and without EGFR-mutation or ALK rearrangements (referred to as EGFR/ALK+). As IMpower010 directly compares atezolizumab with the comparator

relevant in Danish clinical practice, and provides sufficient documentation for efficacy and safety, a literature search for additional evidence has not been performed. Efficacy results, including disease-free survival (DFS) from the interim analysis of IMpower010 (January 21, 2021) and overall survival (OS) from the DFS interim analysis (January 21, 2021) and the first pre-specified OS interim analysis (April 18, 2022), are reported for the subpopulation with stage II–IIIA NSCLC tumours and PD-L1 ≥50% of TC excluding patients with EGFR/ALK+. Safety outcomes, including adverse events (AEs) by severity, serious AEs (SAEs) and discontinuation due to AEs, are reported for the safety-evaluable population and the subpopulation with stage II–IIIA NSCLC tumours and PD-L1 ≥50% of TC. In addition, a qualitative description of the safety profile for adjuvant atezolizumab is included.

RESULTS: IMpower010 met its primary endpoint at the DFS protocol-specified interim analysis, showing a statistically significant and clinically meaningful improvement in DFS for atezolizumab vs. BSC in patients with stage II–IIIA NSCLC whose tumours express PD-L1 on ≥1% of TC. The greatest magnitude of DFS benefit was seen in the PD-L1 TC ≥ 50% subgroups (unstratified hazard ratio (HR) was 0.44 (95% CI, 0.27 to 0.71; p=0.0007) for the subgroup excluding EGFR/ALK+). At the time of follow-up, median DFS could not be estimated for the atezolizumab arm and was 37.3 months (95% CI, 30.1 to not estimable (NE)) in the BSC arm. A significantly higher proportion of patients remained disease-free at 3 years in the atezolizumab arm (75.1%) than in the BSC arm (50.4%). Similar results were observed in the subgroup including EGFR/ALK+. Importantly, exploratory analyses at the first clinical cut-off (DFS interim analysis) suggested an OS benefit of atezolizumab vs. BSC in the PD-L1 TC ≥ 50% subgroup excluding EGFR/ALK+ (unstratified HR was 0.36 (95% CI, 0.17 to 0.75; p=0.0045)). Median OS could not be estimated in either arm. At 3 years, a higher proportion of patients were alive in the atezolizumab arm (91.1%) compared to the BSC arm (76.4%). The result from the OS interim analysis (April 18, 2022) showed a continued clinically relevant OS benefit of atezolizumab (unstratified HR was 0.42 (95% CI, 0.23 to 0.78, p=0.0045)). Data on quality of life was not collected in the study, and is therefore not included in the application.

The safety profile for adjuvant atezolizumab was tolerable and consistent with the previously reported profile for atezolizumab monotherapy across multiple indications and lines of therapy. No new safety signals were observed. In the safety population, grade 3-4 adverse events (AEs) were observed in 21.8% of patients treated with atezolizumab and 11.5% of patients receiving BSC, with grade 5 AEs in 1.6% and 0.6% of patients, respectively. Immune-mediated adverse events (imAEs) were observed in 51.7% of patients treated with atezolizumab and 9.5% of patients receiving BSC. The majority of imAEs were of grade 1-2 (7.9% and 0.6% experienced grade 3–4 AEs in the atezolizumab and BSC arms, respectively). Fewer than 1 in 5 patients (18%) discontinued atezolizumab due to AEs.

CONCLUSION: IMpower010 is the first phase III cancer immunotherapy (CIT) study to demonstrate a DFS improvement in the adjuvant NSCLC setting after cisplatin-based chemotherapy. The data demonstrates a positive benefit-risk profile for atezolizumab in this patient population and supports the indication for atezolizumab as adjuvant treatment following complete resection and platinum-based chemotherapy for patients with NSCLC at high risk of recurrence (stage II–IIIA) whose tumours have PD-L1 expression on ≥50% of TC and who do not have EGFR/ALK+ NSCLC. Atezolizumab therefore represents a significant advancement within the treatment area.

4.3 Health economic assessment

METHODS: A cost-effectiveness model was developed in Microsoft Excel® to assess the cost-effectiveness of atezolizumab vs. BSC for adult patients with stage II-IIIA, early NSCLC with PD-L1 expression ≥50%, who do not have EGFR/ALK+ NSCLC. A five-health-state cohort model structure was implemented through a Markov approach informed by data from the Impower010 trial and other external data sources [1,2]. Model outcomes include life years (LYs), quality-adjusted life years (QALYs), costs of drug acquisition, administration, follow-up costs, AE management, cost

per LY gained and cost per QALY gained. Deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were used to investigate the uncertainty of the model parameters.
As per the Danish Medicines Council guidance, the cost-effectiveness analysis takes a restricted societal perspective, using the best available clinical and economic evidence. Local Danish data inputs are used wherever available. The current model is based on results from the Impower010 study with a follow-up period of five years with the latest data cut from January 2021 [1,2].

RESULTS: In the base case analysis, atezolizumab resulted in increased QALYs gained in comparison to BSC. Costs associated with atezolizumab were also higher compared to BSC for the health state DFS, but saves costs in comparison, in patients in all following health states "Metastatic recurrence (first line (1L))" and "Metastatic recurrence (second line (2L))". This can be explained by the significantly higher proportion of patients remaining in the DFS health state in the intervention arm vs. the comparator, underlining the new intervention's effectiveness. The base-case ICER resulted in [redacted] per QALY.

Based on the projected uptake of atezolizumab as an adjuvant treatment for NSCLC patients with PD-L1 expression ≥50% in the case that atezolizumab receives a positive reimbursement recommendation, the annual budget impact the first five years are:[redacted]

CONCLUSION: Based on the analysis, atezolizumab is a cost-effective use of Danish health care resources, for patients with stage II-IIIA early NSCLC and PD-L1 ≥50% without EGFR/ALK+. Probability analyses were also performed to inform about decision uncertainty at various Willingness-to-Pay (WTP) threshold levels. Assuming a WTP of 425,000 DKK, treatment with atezolizumab is cost-effective in the majority of the simulations, showcased by incremental cost-effectiveness ratios (ICERs) located in the Northeast quadrant of the cost-effectiveness-plane.

5. The patient population, the intervention and choice of comparator

5.1 The medical condition and patient population

Lung cancer is the most deadly cancer disease in Denmark. In 2021, 4,973 Danish patients were diagnosed with lung cancer [3] making the disease one of the most frequent cancer diseases [4]. Approximately 85% of the diagnosed patients have NSCLC and among these patients, approximately 50% have localised (stage I and II) or locally advanced (stage III) disease at the time of diagnosis [3]. These patients can be further divided according to histology, driver mutations (e.g. EGFR-activating mutations in exons 18 through 21 and rearrangements in the ALK), and PD-L1 status.

Early stage NSCLC cancer is typically asymptomatic, with relatively few disease-related symptoms. In Denmark it is defined that for one or more of the following symptoms in persons over 40 years of age with relevant tobacco anamnesis, lung cancer may be suspected and the doctor should consider referring to computed tomography (CT) scans with contrast of thoracic and upper abdomen [5]:

- Cough of more than 4-6 weeks duration in a previously pulmonary injury person or changes in the coughing pattern of a person with chronic bronchitis
- Newly arrived shortness of breath with abnormal spirometry with no other obvious explanation for this
- Haemoptysis (regardless of age) and tobacco anamnesis
- Stridor of unknown cause should lead to CT of thoracic and upper abdomen, spirometry and laryngo-bronchoscopy

- General symptoms in the form of fatigue, lack of appetite, weight loss, thrombocytosis
- Other symptoms of lung cancer may be sputum, chest pain, pneumonia, pleural effusion, stokes collar, neuropathy, bone pain and drumstick fingers, shoulder pain
- Hoarseness of more than 3-4 weeks duration without other accompanying symptoms may be a symptom of lung cancer, however, should be examined primarily by an otologist on suspicion of larynx cancer.

If lung cancer is suspected, the patient is referred to ”lungekræft i pakkeforløb” [5].

The earlier the stage at the time of diagnosis, the better the prognosis. In Denmark early stage NSCLC is treated surgically with curative intent. For patients with stage I, NSCLC surgical treatment alone is the standard of care. For stage II-III there is a higher risk of recurrence and therefore resected patients in these stages are referred to the oncological departments for assessment on eligibility for adjuvant chemotherapy. Patients with stage IB with a tumour diameter of > 4 cm should also be considered referred to the oncological department [6].

In Denmark, the current standard adjuvant treatment is four series of platinum doublet, which should be initiated within 6-8 weeks after surgery. This to reduce the risk of micrometastases and improve survival outcomes compared to surgery alone. The standard of care is cisplatin and vinorelbine, but if the patient is not fit for cisplatin this can be substituted with carboplatin [6]. In 2021, approximately 22% of NSCLC patients undergoing surgery received adjuvant oncological treatment and it is expected that the number of patients receiving multimodal treatment in the early setting will increase in the coming years due to the expected introduction of immunotherapy [3]. According to a Danish expert within the field, the patients receiving adjuvant chemotherapy in Denmark will correspond to the stage II-IIIA population of the IMpower010 study.

In 2021, 1,248 Danish patients underwent resection for their lung cancer [3]. In the same year, the five-year survival rate after surgery was assessed to be 61.7% [3]. For patients undergoing resection at least 9 out of 10 are alive 1 year after surgery, at least 4 out of 5 are alive after 2 years and 3 out of 5 are alive after 5 years [3]. Based on numbers from 2010-2012 the five-year survival rate of Danish lung cancer patients diagnosed with loco-regional disease ranges from 43% for patients with stage I lung cancer, through 27% for stage II to 10% for patients with stage III disease [7]. Therefore, there is still a high unmet need for these patients. The IMpower010 study of adjuvant atezolizumab was the first study to demonstrate that adjuvant immunotherapy can improve disease-free survival (DFS) in a subset of patients and Danish experts have stated that this treatment regime could fit into a Danish setting and thereby offer a valuable benefit for Danish patients with high risk of relapse after surgery.

5.1.1 Patient populations relevant for this application

The Danish patient population expected to be candidates for adjuvant atezolizumab is resected NSCLC patients with a high risk of recurrence with a PD-L1 expression ≥50% and without EGFR/ALK+, who have received adjuvant platinum-based chemotherapy.

High risk of recurrence

The following selection criteria define patients with high risk of recurrence who are included in the therapeutic indication and are reflective of the patient population with stage II-IIIA according to the 7th edition staging system:

- Tumour size ≥ 5 cm; or tumours of any size that are either accompanied by N1 or N2 status; or tumours that are invasive of thoracic structures (directly invade the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve the main bronchus < 2 cm distal to the

carina but without involvement of the carina; or tumours that are associated with atelectasis or obstructive pneumonitis of the entire lung; or tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary.

The study did not include patients who had N2 status with tumours invading the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, or with separate tumour nodule(s) in a different ipsilateral lobe [8].

When the IMpower010 study started (first patient enrolled in 2015), the staging criteria used for inclusion in the trial were based on the most current version available at that time (i.e., the 7th edition UICC TNM classification). The 8th edition was published in 2016 [9]. No modifications were made to the IMpower010 study inclusion criteria (i.e., staging remains based on the 7th edition). Key changes between the 7th and 8th editions are available in Appendix L.

Biomarkers

In Denmark according to guideline the recommendation is to reflex test the following mandatory biomarkers at the primary diagnosis:

- EGFR, ELK, ROS1: adenocarcinoma plus non-small cell carcinoma, where the type cannot be definitely decided [5]
- PD-L1: all non-small cell carcinoma [10].

In minutes from a DaLuPa meeting in January 2022 it is stated that reflex testing for EGFR, ALK, ROS1, BRAF, KRAS and PD-L1 is recommended up-front at primary diagnosis for non-squamous NSCLC [11]. This to determine suitability for treatment with immunotherapy and targeted therapies. MET14 skipping, NTRK1/2/3 and RET is also stated as future biomarkers as treatments are emerging for these targets as well.

As more treatments emerge in the early setting in the coming years testing in this setting will become increasingly important in the future. E.g. Osimertinib (Tagrisso) is currently under evaluation in early lung cancer with EGFR mutations [12]. Please refer to section 5.3.1 for further information on assay or antibody in connection to PD-L1 testing in Denmark.

PD-L1, EGFR and ALK status in the early setting has not been reported in the recent yearly report by the Danish Lung Cancer Group (DLCG) from the Danish Lung Cancer Registry (DLCR) [3]. However, relevant numbers for PD-L1 expression using the 22C3 antibody have been reported from a prospective, consecutive study from the Capital Region of Denmark covering an inclusion period of 10 months [13]. These are in alignment with the numbers seen in IMpower010 for PD-L1 expression in stage II and III. Please refer to Appendix C for further information.

An estimate of the incidence of patients receiving adjuvant chemotherapy in the past 5 years is presented in Table 1 [based on DLCR reports from 2017 to 2021 [3,14–16] and clinical expert opinion]. An estimate of the number of Danish patients eligible for immunotherapy in the adjuvant setting in the 5 coming years is presented in Table 2 [based on the most recent DLCR report [3], clinical expert opinion, and IMpower010]. There are currently studies ongoing in the (neo-)adjuvant setting on Danish sites resulting in a lower number of eligible patients (e.g. NCT04385368 [17]). The patient numbers in the coming years are also dependent on potential EMA approvals in the neoadjuvant setting, e.g. nivolumab [18].

Table 1: Incidence in the past 5 years

Year	2017	2018	2019	2020	2021
Number of resections (all pathologies) [3]	1067	1172	1194	1147	1248
Number of NSCLC patients receiving adjuvant therapy [3,14–16] *	316	319	281	300	273
Number of patients receiving adjuvant medical therapy (chemotherapy) §	278	273	255	261	244

Abbreviations: NSCLC - non-small cell lung cancer. * According to expert statements this is the stage II-IIIA NSCLC patients. § Numbers correspond to 88.0%, 85.6%, 90.7%, 87.0% and 89.4% of patients receiving adjuvant therapy in 2017 [14], 2018 [15], 2019 [16], 2020 [16] and 2021 [3], respectively.

Table 2: Estimated number of patients eligible for treatment

Year*	2022	2023	2024	2025	2026
Number of patients with PD-L1 ≥50% expression *	61 ¤	65	70	75	80
Number of patients with EGFR mutation or ALK rearrangement *	6	6	6	7	7
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years §	**55**	**59**	**64**	**68**	**73**

Abbreviations: ALK - Anaplastic lymphoma kinase; EGFR - Epidermal growth factor receptor; PD-L1 - Programmed death-ligand 1. * PD-L1, EGFR and ALK has not been reported in early setting in Denmark, so the numbers are estimated based on the assumption that 25% of patients receiving adjuvant medical therapy have PD-L1 ≥50%, and of those 6% have EGFR mutations and 3% have ALK rearrangements as the population in IMpower010 [19]. The estimate for PD-L1 is confirmed in a Danish study of patients with NSCLC in the Capital Region of Denmark [13]. ¤ The number is calculated based on the number of patients receiving adjuvant medical therapy in 2021 (n=244) [3]. § Numbers are expected to increase in the coming years depending on national screening initiatives etc. The numbers are also highly dependent on the changing landscape in the neoadjuvant setting.

5.2 Current treatment options and choice of comparator

5.2.1 Current treatment options

The current standard of care in Denmark is four series of cisplatin and vinorelbine. If the patient is not fit for cisplatin this can be substituted with carboplatin [5]. Treatment should be initiated within 6-8 weeks after surgery.

Adjuvant platinum-based combination chemotherapy results in a modest 4-5% improvement in survival vs. observation [6,20,21]. Over a follow-up of approximately 5 years, the percentage of patients who have disease recurrence or who die after surgery remains high ranging from approximately 35% among patients with stage IB disease to 65% among those with stage III disease, regardless of the use of perioperative chemotherapy [9]. Therefore there is a need to improve outcomes in early stage lung cancer.

With the successful development of CIT in advanced NSCLC, anti-PD-L1/PD-1 inhibitors such as atezolizumab, nivolumab, pembrolizumab, and durvalumab may improve upon the modest survival benefit of platinum-based chemotherapy alone in the adjuvant setting when combined and/or sequentially administered with platinum-based chemotherapy. All agents have recently presented positive data in the early NSCLC setting for DSF, event-free survival (EFS) and pathologic complete response (pCR), respectively [pembrolizumab: [22]; nivolumab: [23]; durvalumab: [24]]. No mature OS data has been presented to date.

5.2.2 Choice of comparator

Since there are no approved medicines for adjuvant treatment following resection and platinum-based chemotherapy in early stage NSCLC, the most appropriate comparator considered in the assessment is BSC.

5.2.3 Description of the comparator

BSC includes observation and regular scans for disease recurrence.

5.3 The intervention

With the successful development of CIT in advanced NSCLC, PD-L1/PD-1 inhibitors may improve the modest survival benefit of platinum-based chemotherapy alone in the adjuvant setting. Tecentriq is the first immunotherapy approved in the adjuvant setting after standard chemotherapy. The indication is based on the randomised phase III study, IMpower010. The indication was restricted to patients with stage II-IIIA (7th edition AJCC), PD-L1 expression ≥50% and without EGFR or ALK mutations based on clinical interpretation from subgroup analyses of DFS and OS, indicating that the overall treatment effect observed were largely driven by this subgroup.

5.3.1 Diagnostic

PD-L1 expression

To be eligible for treatment with atezolizumab the patient must have a PD-L1 expression ≥50% of TC and no EGFR mutant or ALK-positive NSCLC. In Denmark all patients with newly diagnosed NSCLC are required to have a PD-L1 analysis on available material at the primary tissue or cellular diagnostics. This is standard at all Danish pathology departments. The examination is performed by immunohistochemistry using the 22C3 antibody [5,10]. In the IMpower010 study originally the SP142 assay was used during screening and enrolment, but in line with the changing landscape of PD-L1 testing, the SP263 PD-L1 immunohistochemistry assay was used to define the primary analysis population. DLCGs pathology guidelines state high accordance between SP263 and the Danish standard 22C3 [10].

According to the SmPC a validated assay should be used to assess PD-L1 expression [8].

Driver mutations

EGFR, ALK and ROS1 analysis is performed on all new patients using preferably NGS analysis and if not available IHC and FISH analysis. The tendency is that NGS panels are replacing IHC and FISH in this setting [25].

5.3.2 Dosing

The recommended dose of atezolizumab is either 840 mg administered intravenously every two weeks, or 1200 mg administered intravenously every three weeks, or 1680 mg administered intravenously every four weeks. The

recommended duration of treatment is 1 year unless disease recurrence or unacceptable toxicity. Treatment duration for more than 1 year was not studied.

5.3.3 Monitoring and follow-up

During treatment the patients should be monitored for symptoms of immune-related reactions as described in the SmPC [8].

In the IMpower010 study tumours were assessed with CT of the chest and upper abdomen in all patients at baseline, and every 4 months in the first year and every 6 months in the second year. Patients without disease recurrence continued disease status assessments with alternating chest CT and x-ray every 6 months during years 3-5, and annually by x-ray thereafter. Additional scans could be performed if recurrence of disease was suspected. To ensure the same frequency of study assessments between the treatment arms, including assessments for disease recurrence and safety, patients in the BSC arm were required to undergo medical contact every 3 weeks for assessments during the first year for symptom and AE assessment.

Atezolizumab should be initiated after chemotherapy. In Denmark, the follow-up of patients in and after adjuvant chemotherapy is described in DLCGs guideline and states that follow-up after curative-intended treatment should be initiated due to tracing of therapeutic complications, relapse and new primary lung cancer. Follow-up is recommended every 3 months for two years and then every six months for a total 5-year control process. Patients who are not candidates for adjuvant therapy or postoperative radiotherapy may transition directly to the follow-up course [6].

Currently local studies e.g. the SUPE_R study [26] is investigating new potential ways of improving patient follow-up in the early lung cancer setting with positron emission tomography combined with computer tomography (PET/CT) and potentially use of circulating tumour DNA (ctDNA).

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

The clinical phase III study IMpower010 directly compares atezolizumab with the comparator relevant in Danish clinical practice. The study provides sufficient documentation for efficacy and safety for both the intervention and comparator, and therefore, a literature search for additional evidence has not been performed.

Results for the main study population in the trial are published in a peer-reviewed publication [19]. Data for the subpopulation of patients with stage II–IIIA tumours with PD-L1 expression of ≥50% of TC without EGFR/ALK+ are available in either Felip et al. 2021 [19] and/or EMA's assessment report and SmPC for atezolizumab [8,27]. Data on certain outcomes in the subpopulation are not yet published [28].

6.2 List of relevant studies

The included study is listed in Table 3 below. For detailed information about the study refer to appendix B.

Table 3: Relevant study included in the assessment

Reference	Trial name	NCT number	Dates of study	Used in comparison of
Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Felip et al. The Lancet. 2021.	IMpower010	NCT02486718	Start date: October 31, 2015 Expected completion date: December 17, 2027	Atezolizumab vs. BSC for NSCLC patients with stage II-IIIA disease following complete resection and platinum-based chemotherapy and with PD-L1 expression of ≥ 50% of TC and without EGFR mutations or ALK rearrangements.

Abbreviations: ALK - anaplastic lymphoma kinase; BSC – best supportive care; EGFR - epidermal growth factor receptor; NSCLC - non-small cell lung cancer; PD-L1 - Programmed death-ligand 1.

7. Efficacy and safety

7.1 Efficacy and safety of atezolizumab compared to best supportive care for NSCLC patients with stage II-IIIA disease following complete resection and platinum-based chemotherapy and with PD-L1 expression of ≥ 50% of TC and without EGFR/ALK+

7.1.1 Relevant studies

In the following section, we provide a brief description of the study included in the assessment (Table 3). For detailed study characteristics refer to appendix B. For demographics and baseline characteristics of patients included in the study refer to appendix C.

7.1.1.1 IMpower010 (NCT02486718)

IMpower010 is a randomised, multicentre, open-label, phase III study designed to investigate the efficacy and safety of adjuvant treatment with atezolizumab compared to BSC in adults patients with stage IB-IIIA NSCLC following resection and adjuvant chemotherapy. The study is conducted at 227 sites in 22 countries and regions, and is currently ongoing.

The study comprises an enrolment phase and a randomisation phase. During the enrolment phase of the study, eligible patients underwent surgical resection followed by up to 4 cycles of adjuvant cisplatin-based chemotherapy. Each cycle was 21 days in length and consisted of 1 of the following investigator-selected regimens:

- Cisplatin 75 mg/m2 IV on Day 1 plus 1 of the following:
  - Vinorelbine 30 mg/m2 IV push, Days 1 and 8
  - Docetaxel 75 mg/m2 IV, Day 1
  - Gemcitabine 1250 mg/m2 IV, Days 1 and 8
  - Pemetrexed 500 mg/m2, Day 1 (non-squamous NSCLC only)

After completion of adjuvant cisplatin-based chemotherapy, patients without disease progression who still met eligibility criteria (n=1005) were randomly assigned in a 1:1 ratio by a permuted-block method (block size of four) to

receive adjuvant atezolizumab 1200 mg IV every 21 days for 16 cycles (n=507) or BSC (observation and regular scans for disease recurrence) (n=498). Patients were stratified based on gender, stage of disease (IB vs. II vs. IIIA), histology, and PD-L1 tumour expression status as assessed via SP142 assay (TC 2/3 and any IC vs. TC0/1 and IC2/3 vs. TC0/1 and IC0/1).

In a protocol amendment on February 11, 2020, almost 1 year before this interim analysis was done and after all patients had been randomly assigned, the PD-L1 subpopulation to be analysed for DFS was amended to patients whose tumours expressed PD-L1 on 1% or more of TC as defined by the SP263 assay in the stage II–IIIA population [19]. This was done in line with the changing landscape of PD-L1 testing.

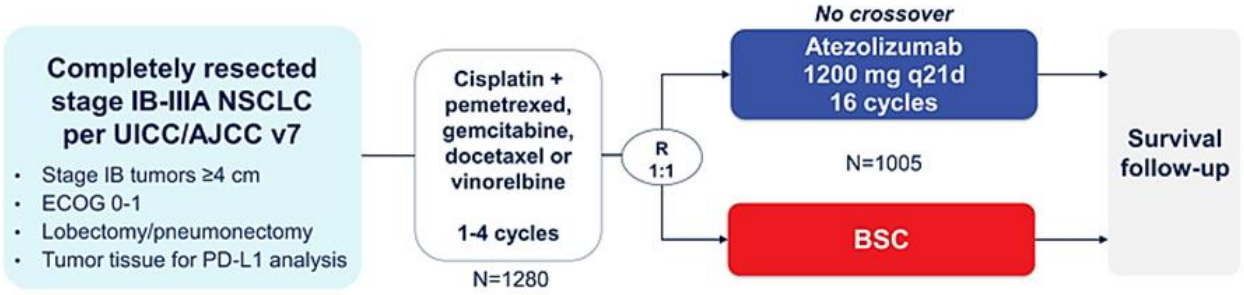


Figure 1: IMpower010 study design

Abbreviations: BSC - best supportive care; ECOG - Eastern Cooperative Oncology Group; N - number of patients; NSCLC - Non-small cell lung cancer; PD-L1 - programmed death-ligand 1; q21d - every 21 days; R - randomisation; UICC/AJCC - Union for International Cancer Control/American Joint Committee on Cancer.

The primary efficacy endpoint was DFS assessed by investigator. The endpoint was tested hierarchically first in the stage II-IIIA population subgroup whose tumours expressed PD-L1 on 1% or more of TC (SP263), then all patients in the stage II–IIIA population, and finally the intention-to-treat (ITT) population (stage IB-IIIA). The secondary efficacy endpoints were overall survival (OS) in the ITT population, DFS in patients with stage II–IIIA tumours and PD-L1 ≥50%, and 3- and 5-year DFS rates in all three primary analysis populations. Exploratory endpoints of relevance for this assessment include 3- and 5-year DFS rates, OS in patients with stage II–IIIA tumours and PD-L1 ≥50%, and DFS and OS in patients with stage II–IIIA tumours and PD-L1 ≥50% without EGFR/ALK+.

Safety was evaluated in all patients who either received at least one dose of atezolizumab or who were randomised to the BSC arm and had at least one post-baseline assessment. Patient-reported outcome (PRO) instruments were not included in the IMpower010 study.

7.1.2 Efficacy and safety – results per study

IMpower010 provides a direct comparison between atezolizumab and BSC and the results can be used to address the clinical question. In the following section, we provide a summary of the key efficacy and safety findings for the study. Data on the following outcomes have been extracted:

- Disease-free survival
- Overall survival
- Safety

- Incidence of AEs by severity, serious AEs (SAEs) and discontinuation due to AEs
- Qualitative description of the safety profile of atezolizumab

For the efficacy outcomes, we present data for the subgroup of patients with stage II–IIIA tumours and PD-L1 ≥50% without EGFR/ALK+. For safety outcomes, we present data for the safety population and the subpopulation with stage II–IIIA tumours and PD-L1 ≥50%. The data presented are from the clinical cut-off date (CCOD) of January 21, 2021 and the CCOD of April 18, 2022 (OS interim analysis only). For detailed efficacy and safety results, refer to appendix D.

At the time of study design, it was decided not to collect PROs given the potential difficulty in demonstrating impact on quality of life in a largely asymptomatic patient population that was not receiving an active control therapy. As a result PRO instruments were not included in IMpower010, and therefore data on quality of life is not included in the application.

7.1.2.1 Disease-free survival

The primary efficacy outcome measure of IMpower010 was investigator-assessed DFS defined as the time from randomisation to the date of first documented recurrence of NSCLC, occurrence of new primary NSCLC, or death from any cause, whichever occurred first. DFS as a surrogate for OS is an accepted endpoint for drug approval by both the EMA and the FDA, as demonstrated with the approval of immune checkpoint inhibitors for adjuvant treatment of several solid tumours, including melanoma, renal cell carcinoma and muscle-invasive bladder cancer [29]. DFS is the endpoint in most studies in early NSCLC [30].

Data for patients who were not reported as experiencing disease recurrence, a new primary NSCLC, or death were censored at the date of the last tumour assessment. If no post-baseline data were available, DFS was censored at the date of randomisation. If recurrence of disease or new primary NSCLC prior to randomisation was documented, DFS was censored at the date of randomisation. HR was estimated with use of a stratified Cox regression model, including a two-sided 95% confidence interval (CI). The stratification factors used for the analysis were stage (IB and II combined vs. IIIA), sex (female vs. male), histology (squamous vs. non-squamous), and PD-L1 tumour expression status by SP142 IHC assay ([TC2/3 and any IC, TC0/1 and IC2/3 combined] vs. TC0/1 and IC0/1). Kaplan-Meier methodology was used to estimate the median DFS for each treatment arm and the Kaplan-Meier curve was constructed to provide a visual description of the difference between the treatment and control arms. Brookmeyer-Crowley methodology was used to construct the two-sided 95% CI for the median DFS for each treatment arm. 3- and 5-year landmark DFS rates were estimated by Kaplan-Meier methodology, and the Greenwood's formula were used to establish the 95% CIs.

After all patients had been randomly assigned, the PD-L1 subpopulation to be analysed for DFS was amended to patients whose tumours expressed PD-L1 on 1% or more of TC as defined by the SP263 assay in the stage II–IIIA population (protocol amendment on February 11, 2020) [19].

At the time of the interim DFS analysis (CCOD January 21, 2021), the study showed a statistically significant improvement in DFS in the atezolizumab arm compared to the BSC arm in the PD-L1 ≥1% TC (SP263) stage II-IIIA patient population, thereby meeting the primary endpoint of the study. At this time, the results in the other primary analysis populations, the all randomised (stage II-IIIA) population and the ITT (stage IB-IIIA) population, did not cross the significance boundary [19]. In addition to the three primary analysis populations in the study, a key pre-defined secondary analysis was based on the subpopulation with stage II–IIIA tumours and PD-L1 ≥ 50% per SP263 IHC assay. In addition, an analysis based on the same subpopulation, but excluding patients with known EGFR mutations or ALK rearrangements, was conducted. Data for this subpopulation is the basis for the EMA approval and is presented in the following. Both stratified and unstratified DFS HRs are available and will be presented, but main emphasis will be

placed on the unstratified HR given that the inclusion of the stratification factors in the Cox regression was not planned in the statistical analysis plan for the PD-L1 ≥50% stage II-IIIA population without EGFR/ALK+. Analyses in subgroups normally present unstratified HRs, since accounting for several stratification factors in each subgroup may not be applicable or feasible with reduced sample sizes. Results from the stratified HR analyses were included in the SmPC upon request from EMA.

PD-L1 TC ≥50% stage II–IIIA population without EGFR/ALK+

At data cut-off, the median duration of follow-up for the DFS analysis was 34.2 months in the PD-L1 ≥50% stage II-IIIA population without EGFR/ALK+. At this time, 24 (22.6%) of 106 patients in the atezolizumab arm and 45 (43.7%) of 103 in the BSC arm had experienced disease recurrence or death; the unstratified HR was 0.44 (95% CI, 0.27 to 0.71; p=0.0007) [27] (Table 4). The stratified analysis showed results similar to the unstratified analysis (HR: 0.49 (95% CI, 0.29 to 0.81, p=0.0045) [8,27]); the differences between the HRs are small, the CIs overlap and do not include 1. The median DFS could not be estimated for the atezolizumab arm and was 37.3 months (95% CI, 30.1 to NE) in the BSC arm per Kaplan-Meier analysis [8,27].

A significantly higher proportion of patients remained disease-free at 3 years in the atezolizumab arm (75.1%; 95% CI, 65.4 to 84.8) than in the BSC-treated arm (50.4%; 95% CI, 39.2 to 61.7) with a difference in rate of 24.7% (95% CI, 9.8 to 39.5; p=0.0011) [8,27] (Table 4, Figure 2). The disease-free rate at 5 years could not be estimated in either arm [27].

Overall, the results were similar to those in the PD-L1 TC ≥50% stage II-IIIA population (including EGFR/ALK+). Results for this population can be found in Appendix L. Moreover, subgroup analyses in the PD-L1 TC ≥50% stage II-IIIA population and the PD-L1 TC ≥50% stage II-IIIA population without EGFR/ALK+ by baseline characteristics and biomarker status demonstrated that a benefit in DFS was generally observed across key subgroups in patients treated with atezolizumab compared with BSC, including patients who received 4 cycles of cisplatin plus vinorelbine [28], which is the cisplatin-based chemotherapy regimen of choice in Danish practice. Results are presented in Appendix L.

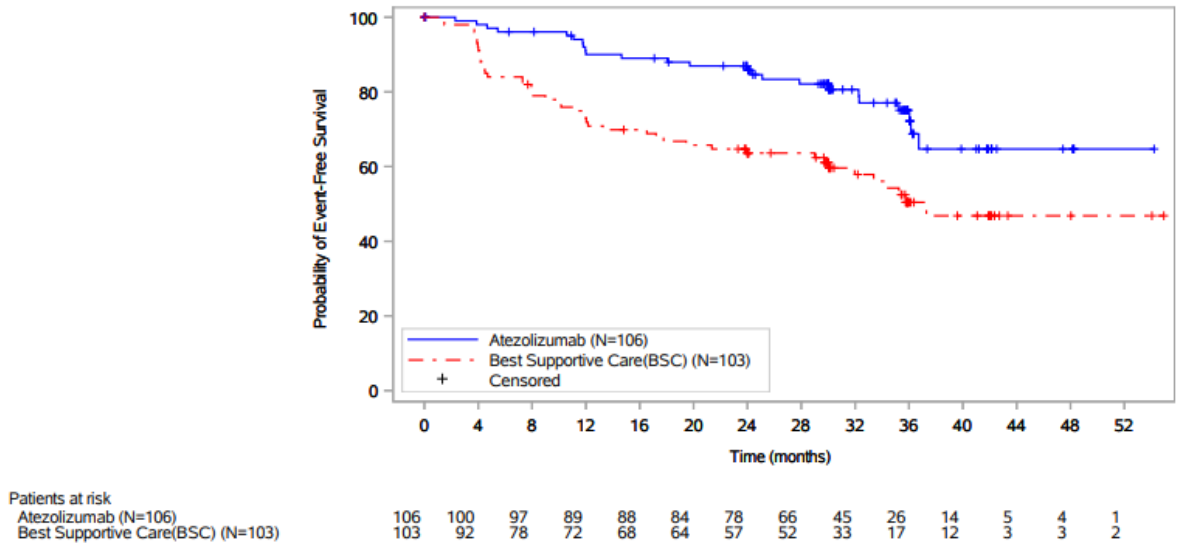


Figure 2: Kaplan-Meier estimate of DFS in the PD-L1 SP263 TC ≥ 50% stage II–IIIA population without EGFR/ALK+

Clinical data cutoff: 21 January 2021. Abbreviations: BSC - best supportive care; DFS - disease-free survival; N - number of patients; PD-L1 - programmed death-ligand 1; TC - tumour cell. Figure available in EMA's assessment report [27].

Table 4: DFS in the PD-L1 SP263 TC ≥50% stage II-IIIA population without EGFR/ALK+

Trial name	Intervention	Median follow-up	N	Patients with event (%)	DFS			
					Median, mo (95% CI)	HR (95% CI)	DFS at 3 years, % (95% CI)	DFS at 5 years, % (95% CI)
IMpower010 [8,27] CCOD Jan 21, 2021	ATZ	34.2 months	106	24 (22.6)	NE (NE-NE)	0.44 (0.27-0.71)	75.1 (65.4-84.8)	NE (NE-NE)
	BSC		103	45 (43.7)	37.3 (30.1-NE)		50.4 (39.2-61.7)	NE (NE-NE)

Abbreviations: ALK - anaplastic lymphoma kinase; ATZ - atezolizumab; BSC - best supportive care; CCOD - clinical cut-off date; CI - confidence interval; DFS - disease-free survival; EGFR - epidermal growth factor receptor; HR - hazard ratio; mo - months; N - number of patients; NE - not evaluable; PD-L1 - programmed death-ligand 1; TC - tumour cells.

7.1.2.2 Overall survival

The key secondary outcome measure of IMpower010 was OS defined as the time from randomisation to death of any cause. Data for patients who were not reported as having died at the date of analysis were censored at the date when they were last known to be alive. If no post-baseline data was available, OS was censored at the date of randomisation.

In addition to the primary analysis population (the ITT population) for OS, additional exploratory OS analyses based on the subpopulation with stage II–IIIA tumours and PD-L1 TC ≥50% per SP263 IHC assay excluding patients with known EGFR mutations or ALK rearrangements were conducted using the same methodology as applied for DFS. Data from an early OS analysis, which were conducted at the time of the DFS interim analysis, and the first prespecified interim OS analysis for this subpopulation is presented below. As for DFS, both stratified and unstratified OS HRs are available, but main emphasis will be placed on the unstratified HR.

PD-L1 TC ≥50% stage II–IIIA population without EGFR/ALK+

At the time of the interim DFS analysis (CCOD January 21, 2021), an OS benefit was observed in the atezolizumab arm compared to the BSC arm; the unstratified HR was 0.36 (95% CI, 0.17 to 0.75; p=0.0045) [27] (Table 5). The stratified analysis showed results similar to the unstratified analysis (HR: 0.39 (95% CI, 0.18 to 0.82, p=0.01) [8,27]). A higher proportion of patients were alive at 3 years in the atezolizumab arm (91.1%; 95% CI, 85.0 to 97.1) compared to the BSC arm (76.4%; 95% CI, 67.6 to 85.1) with a difference in rate of 14.7% (95% CI, 4.1 to 25.3; p=0.0067) [27] (Table 5, Figure 3). The OS rate at 5 years could not be estimated in either arm [27].

Overall, the results were similar to those in the PD-L1 TC ≥50% stage II-IIIA population (including EGFR/ALK+). Results for this population can be found in Appendix L. Moreover, subgroup analyses in the PD-L1 TC ≥50% stage II-IIIA population by baseline characteristics and biomarker status demonstrated that a benefit in OS was generally observed across key subgroups in patients treated with atezolizumab compared with BSC (EMA 2022). Results are presented in Appendix L.

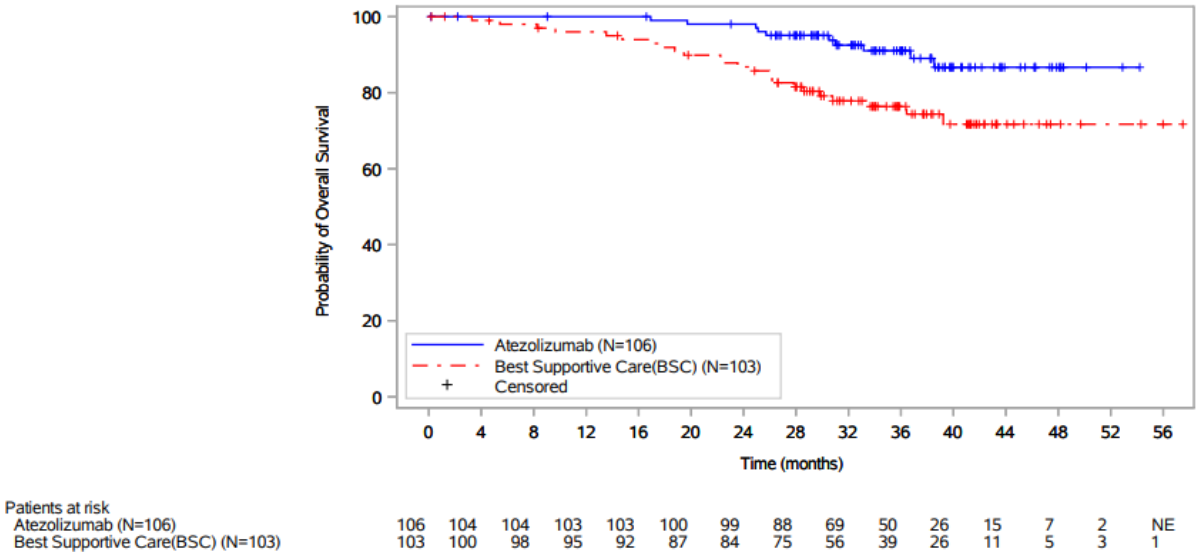


Figure 3: Kaplan-Meier estimate of OS in the PD-L1 SP263 TC ≥ 50% stage II–IIIA population without EGFR/ALK+

Clinical data cutoff: 21 January 2021. Abbreviations: ALK - anaplastic lymphoma kinase; BSC - Best supportive care; EGFR - epidermal growth factor receptor; N - number of patients; NE - not evaluable; OS – overall survival; PD-L1 - programmed death-ligand 1; TC - tumour cells. Figure available in EMA's assessment report [27].

At the time of the first prespecified interim analysis for OS (CCOD April 18, 2022), the unstratified HR for OS was 0.42 (95% CI, 0.23 to 0.78, p=0.0045) in favour of atezolizumab over BSC [31] (Table 5). [redacted] [28]. At the time of CCOD, the 5-year OS rate was 84.8% (95% CI, 77.7 to 91.9) in the atezolizumab arm and 67.5% (95% CI, 57.5 to 77.6) in the BSC arm [31].

The difference in rate was 17.3% (95% CI, 5.0 to 29.6; p=0.0059) [28]. Due to the low rate of death in both study arms, a median OS could not be estimated via Kaplan-Meier analysis for either arm [31]. The results demonstrate a continued clinically relevant OS benefit of atezolizumab.

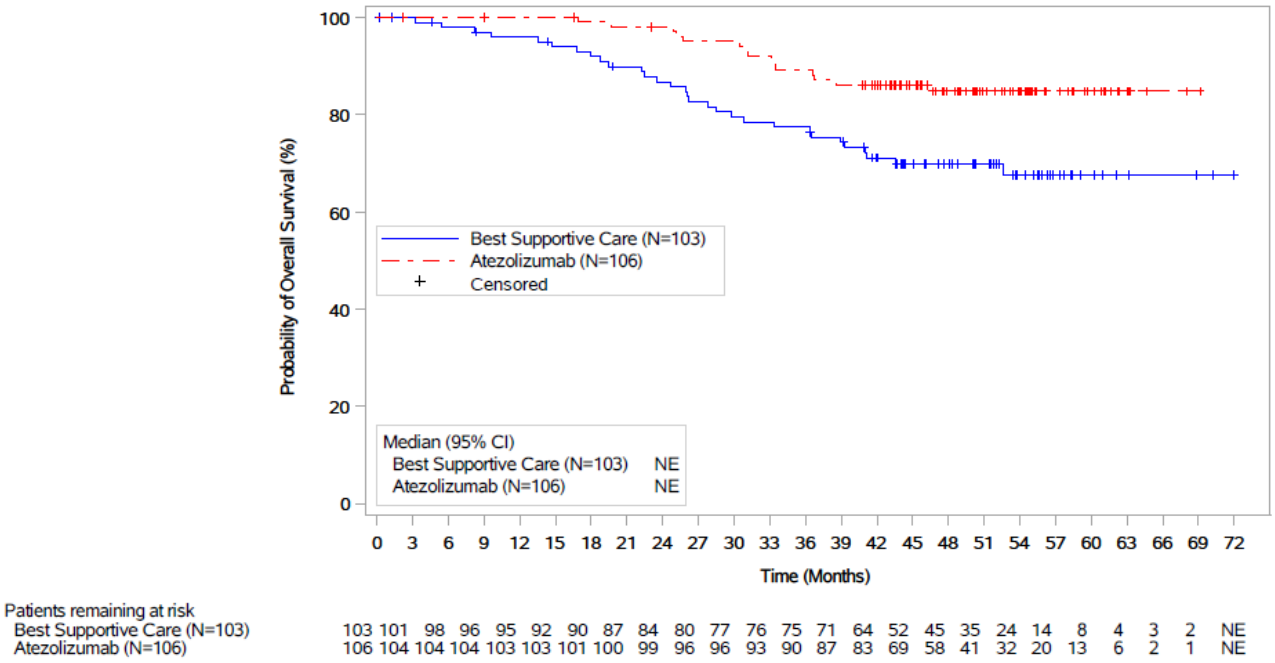


Figure 4: Kaplan-Meier estimate of OS in the PD-L1 SP263 TC ≥50% stage II–IIIA population without EGFR/ALK+

Clinical data cutoff: 18 April 2022. Abbreviations: ALK - anaplastic lymphoma kinase; CI - confidence interval; EGFR - epidermal growth factor receptor; N - number of patients; NE - not evaluable; OS – overall survival; PD-L1 - programmed death-ligand 1; TC - tumour cells. Figure has been presented at the World Conference on Lung Cancer (WCLC) August 6-9 2022 [31].

Table 5: OS in the PD-L1 SP263 TC ≥50% stage II-IIIA population without EGFR/ALK+

Trial name	Intervention	Median follow-up	N	Patients with event (%)	OS			
					Median. mo (95% CI)	HR (95% CI)	OS at 3 years, % (95% CI)	OS at 5 years, % (95% CI)
IMpower010 [8,27] CCOD Jan 21, 2021	ATZ	34.2 months	106	10 (9.4)	NE (NE-NE)	0.36 (0.17-0.75)	91.1 (85.0-97.1)	NE (NE-NE)
	BSC		103	24 (23.3)	NE (NE-NE)		76.4 (67.6-85.1)	NE (NE-NE)
IMpower010 [28,31] CCOD Apr 18, 2022	ATZ	47.7 months	106	15 (14.2)	NE (NE-NE)	0.42 (0.23-0.78)	89.1 (83.1- 95.2)	84.8 (77.7-91.9)
	BSC		103	30 (29.1)	NE (NE-NE)		77.5 (69.2-85.8)	67.5 (57.5-77.6)

Abbreviations: ALK - anaplastic lymphoma kinase; ATZ - atezolizumab; BSC - best supportive care; CCOD – clinical cut-off date; CI - confidence interval; EGFR - epidermal growth factor receptor; HR - hazard ratio; mo - months; N - number of patients; NE - not evaluable; OS - overall survival; PD-L1 - programmed death-ligand 1; TC - tumour cells.

7.1.2.3 Safety

Safety data will be presented in two parts as follows:

- Incidence of AEs by severity, SAEs and discontinuation due to AEs
- Qualitative description of the safety profile of atezolizumab

In this section main emphasis will be on the safety population in IMpower010, including patients with stage IB-IIIA NSCLC that had received at least 1 dose of atezolizumab or patients randomised to the BSC arm with at least 1 post-baseline safety assessment (n=990). Safety data were reported at the clinical cut-off date of January 21, 2021. At this time, the median duration of exposure with atezolizumab was 10.4 months. The median dose intensity of atezolizumab was 100%, with a median number of doses received of 16. In the atezolizumab arm, 65% of patients received the planned 16 doses/cycles.

Incidence of AEs by severity, SAEs and discontinuation due to AEs

An overview of the incidence of safety outcomes in the atezolizumab and BSC arms are presented in Table 6. Overall, the frequency of patients experiencing safety events are higher in the atezolizumab arm, which is to be expected when comparing active treatment to BSC, including observation and scans for disease recurrence. The safety outcomes are described qualitatively in the following section. The safety outcomes observed were similar in the PD-L1 TC ≥50% population (including patients with EGFR/ALK+) [32].

Table 6: Incidence of safety outcomes in the safety population (stage IB-IIIA) and the PD-L1 TC ≥50% stage II-IIIA population

	Stage IB-IIIA		PD-L1 TC ≥50% stage II-IIIA	
Safety parameter	**Atezolizumab n=495**	**BSC n=495**	**Atezolizumab n=113**	**BSC n=112**
Any AE, n (%)	459 (92.7)	350 (70.7)	107 (95)	78 (70)
Grade 3-4 AEs Grade 5 AEs	108 (21.8) 8 (1.6)	57 (11.5) 3 (0.6)	23 (20) 0 (0)	13 (12) 0 (0)
Treatment-related AE, n (%)	335 (67.7)	0 (0)	73 (65)	0 (0)
Grade 3-4 treatment-related AEs Grade 5 treatment-related AEs	53 (10.7) 4 (0.8)	0 (0) 0 (0)	12 (11) 0 (0)	0 (0) 0 (0)
Any SAE, n (%)	87 (17.6)	42 (8.5)	17 (15)	6 (5)
Treatment-related SAE	37 (7.5)	0 (0)	8 (7)	0 (0)

Discontinuation of treatment due to AEs, n (%)	90 (18.2)	N/A	21 (19)	N/A

Abbreviations: AE - adverse event; BSC - best supportive care; n - number of patients; N/A - not applicable; NE - not evaluable; PD-L1 - programmed death-ligand 1; SAE - serious adverse event. Data for the safety population is derived from EMA's assessment report [27] and Felip et al. 2021 [19] and data for the PD-L1 TC ≥50% stage II-IIIA population is derived from Felip et al. 2022 [32]

Qualitative description of the safety profile of atezolizumab

AEs of any grade occurred in 92.7% of patients in the atezolizumab arm and 70.7% in the BSC arm. AEs of any grade with ≥5% difference between the atezolizumab vs. the BSC arm included arthralgia (10.5% vs. 5.3%), pyrexia (13.1% vs. 2.2%), ALAT increased (10.7% vs. 3.2%), ASAT increased (10.7% vs. 3.2%), hypothyroidism (11.1% vs. 0.6%), pruritis (10.3% vs. 0.6%), rash (9.7% vs. 1.0%), diarrhoea (7.5% vs. 1.8%), and hyperthyroidism (6.5% vs. 0.6%) [27].

Grade 3-4 AEs were observed in 21.8% of patients in the atezolizumab arm vs. 11.5% in the BSC arm [19,27]. Grade 3-4 AEs occurring in ≥1% of either arm (atezolizumab arm vs. BSC arm, respectively) included pneumonia (1.4% vs. 0.6%), increased ALAT (1.6% vs. 0.2%), increased ASAT (1.4% vs. 0.0%), rash (1.0% vs. 0.0%) and hypertension (1.0% vs. 0.4%). Between treatment arms there was no difference of ≥2% in grade 3-4 AEs [27]. Grade 5 AEs were observed in 8 patients (1.6%) in the atezolizumab arm and 3 patients (0.6%) in the BSC arm [19,27]. In the atezolizumab arm, 4 (0.8%) were treatment-related and included myocarditis, interstitial lung disease, multiple organ dysfunction syndrome, and acute myeloid leukaemia (compared to 0.3% in the metastatic setting) [27]. All of the related AEs with fatal outcome were single event occurrences and therefore no trends in terms of a safety signal were noted. The AEs with fatal outcomes have been reflected in the [27].

Rates of any grade of immune-mediated adverse events (imAEs) were 51.7% in the atezolizumab arm and 9.5% in the BSC arm. In comparison this was 38.4% in the pooled monotherapy population with advanced disease [8,19,27]. It is possible that patients being treated in the adjuvant setting, being relatively healthier, may be more susceptible to developing imAEs. This is consistent with what has been observed in adjuvant studies of other immune checkpoint inhibitors [27]. The majority of imAEs were grade 1–2, with grade 3–4 accounting for 7.9% of patients in the atezolizumab arm and 0.6% of patients in the BSC arm. Grade 3-4 imAEs in the atezolizumab arm included hepatitis (diagnosis and laboratory abnormalities (4.0%), laboratory abnormalities (3.2%)), rash (1.4%), pneumonitis (0.8%), hyperthyroidism (0.4%), adrenal insufficiency (0.4%), and infusion-related reaction (0.2%) [28].

The frequency of patients experiencing ≥1 SAE in the atezolizumab arm vs. the BSC arm was 17.6% vs. 8.5%, respectively. Of those patients in the atezolizumab arm, SAEs related to atezolizumab treatment occurred in 7.5% [19,27]. The frequency of each SAE related to atezolizumab treatment was <1% when categorised by preferred term. Treatment-related SAEs reported in ≥2 patients included pneumonitis, interstitial lung disease, meningitis, peripheral neuropathy, pyrexia, drug- induced liver injury, hepatitis, and sarcoidosis [28]. Across both arms, most patients with SAEs had their SAEs resolved (83.9%) or resolving at the time (6.9%), unresolved (6.9%) and resolved with sequelae (4.6%) at the time of CCOD [27].

A total of 18.2% of atezolizumab-treated patients discontinued due to an AE, with the most common AEs (≥1%) being pneumonitis (1.4%), hypothyroidism (1.4%), increased ASAT (1.4%), and increased ALAT (1.0%) [19,27]. The rate of discontinuation due to AEs were higher than the rates observed in the pooled atezolizumab monotherapy populations with advanced disease [27]. However, approximately half of the AEs that led to discontinuation in IMpower010 were of grade 1-2, which might indicate that investigators had a lower threshold for discontinuing treatment in patients with early-stage NSCLC due to treatment-related toxicity than might be seen in the metastatic setting [19]. Moreover,

the median treatment duration was longer for patients treated with atezolizumab in the adjuvant setting in IMpower010 (10.4 months) compared with metastatic patients treated with atezolizumab until disease progression or loss of clinical benefit in the pooled monotherapy populations (3.5 months each). The median number of atezolizumab doses administered was 16 in IMpower010 (maximum allowed per protocol) and 6 in the pooled atezolizumab monotherapy populations [27]. Dose interruptions occurred in 28.7% of patients treated with atezolizumab [27]. AEs with a frequency ≥1% leading to atezolizumab dose interruption were hyperthyroidism (2.8%), increased ASAT (1.6%), pyrexia (1.6%), increased ALAT (1.4%), rash (1.4%), upper respiratory tract infection (1.4%), hypothyroidism (1.2%), headache (1.2%), and pneumonia (1.0%) [28].

Conclusion

The safety profile of atezolizumab in the adjuvant setting in the NSCLC population was generally consistent with the overall pooled monotherapy safety profile in the advanced setting and no new safety signals were observed. However, a higher incidence of imAEs and a higher rate of discontinuations due to AEs were observed in IMpower010 compared with the pooled atezolizumab monotherapy population with advanced disease. Consistent with previous observation, patients treated in the adjuvant setting may be more susceptible to developing imAEs [27]. Several factors may affect the rate of discontinuation due to AEs in the adjuvant setting compared to the metastatic setting, including investigator threshold for discontinuing patients, median treatment duration and doses administered.

7.1.3 Comparative analyses of efficacy and safety

The IMpower010 study provides a direct comparison between atezolizumab and BSC and results can be used to address the clinical question. The comparative results for atezolizumab vs. BSC has been presented in section 7.1.2.

8. Health economic analysis

8.1 Model

8.1.1 Model structure

The analysis uses a Markov model structure as this allows consideration of the long-term clinical and economic outcomes associated with early NSCLC. It does not use a partitioned survival model because the IMpower010 data does not contain information on non-death outcomes after recurrence [1,33]. The limitation of not using a partitioned survival model is that the transition probabilities after recurrence remain time-invariant which may not reflect reality. Figure 5 presents the model structure and health states.

Abbreviations: 1L – first-line; 2L – second-line

8.1.2 Health states

8.1.2.1 Disease-free Survival

This is the starting health state in the cost-effectiveness model. Patients in the intervention arm receive atezolizumab for 16 cycles (treatment duration ~ 1 year) and simultaneously follow-up care for a maximum length of 5 years, while those in the best supportive care (BSC) arm receive follow-up care. Patients who have a locoregional or metastatic recurrence, or die transition to the locoregional recurrence, metastatic recurrence, or death health states.

8.1.2.2 Locoregional Recurrence

Patients transition to this health state from DFS if they have locoregional recurrence where they can be treated with curative or palliative intent or not treated. The model uses this separation to account for patients who cannot or may not choose to be treated as this choice will affect the clinical and economic outcomes.
Patients on curative treatment who have metastatic recurrence or who die transition to the metastatic recurrence (1L treatment) or death health states. However, patients on palliative treatment or no treatment can only progress to the death health state.

8.1.2.3 1L Metastatic Recurrence

Patients transition to this health state from DFS and locoregional recurrence if they have a metastatic recurrence and can choose to either be treated or not. The model uses this separation to account for patients who cannot or may not choose to be treated, as this will affect the clinical and economic outcomes.
Patients on treatment who progress or die then transition to the metastatic recurrence (2L treatment) or death health state while those not on treatment can only transition to the death health state.

8.1.2.4 2L Metastatic Recurrence

Patients transition to this health state from metastatic recurrence (1L treatment) if they have disease progression and can choose to either be treated or not. The model uses this separation to account for patients who cannot or may not choose to be treated, as this will affect the clinical and economic outcomes.
Patients can only transition to the death health state. We do not include subsequent lines of metastatic treatment due to the low use and, therefore, minimal impact on the cost per quality-adjusted life year (QALY).

8.1.2.5 Death

Death is an absorbing health state and patients remain in it until the end of the model's time horizon.

8.1.3 Time horizon

The model uses a lifetime horizon of 40 years, considered to represent a lifetime horizon for patients. Given the mean age of 61 years in the IMpower010 trial, 40 years was considered a fair approximation of a lifetime time horizon [1,33].

8.1.4 Cycle length, discounting, half-cycle correction

A limitation with Markov models is that time is discrete. Thus, they allow patients to transition across health states only once per model cycle which may not be consistent with reality as they may occur continuously. The model uses a cycle length of 1 month to deal with this issue as we can expect any differences in the timing of transitions between the model and reality to be smaller with shorter cycle lengths and applies half-cycle corrections assuming that transitions across health states occur mid-cycle on average:

$$Survival_t = (survival_t + survival_{t+1})/2$$

A discount rate of 3.5% until year 35 and 2.5% beyond year 35 was applied to costs and efficacy, as defined by the Danish Ministry of Finance and in the DMC guidelines [34,35].

8.1.5 Economic perspective

The current analysis is performed from a restricted societal perspective in line with the DMC guidelines [34]. This implies consideration of costs directly related to the treatment of the disease and its medical consequences.

Moreover, patient costs, patient time and travel costs are included in the analysis. Indirect costs due to productivity losses are not considered in the analysis.

8.1.6 Key assumptions

The model was developed based on the clinical and treatment pathways for adult patients with stage II-IIIA, Early Non-Small Cell with PD-L1 expression ≥50%, who are EGFR and ALK+ mutation-negative; consideration of key clinical aspects (DFS, locoregional recurrence, 1L metastatic recurrence, 2L metastatic recurrence, and OS) that affect clinical outcomes, costs, and treatment decisions; a thorough review of published economic modelling approaches and available HTA submission reports was used to validate the model approach. For validation of model inputs and structural assumptions, Danish clinical experts within the area of NSCLC were consulted together with a review of Danish treatment guidelines. The model approach is in line with the approach accepted by DMC in the assessment of trastuzumab emtansine for early HER2+ breast cancer [8]. Similar to the model for trastuzumab emtansine, this model relies on external data to inform the transition probability from the states not directly captured within the trial, i.e., the transition probability from locoregional disease, 1L metastatic recurrence, and 2L metastatic recurrence.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

Table 7 below presents some of the key parameters used in the health economic model and how these have been obtained. Further description of model parameters can be found in section 8.3.

Table 7: Input data used in the model base case

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated**
Disease-free survival (DFS)	See section 8.3.1. Based on IMpower010 subgroup: PD-L1 ≥50%, Stage II-IIIA, excl. EGFR and ALK+. Observed DFS curves for treatments included in the Impower010 trial (i.e., atezolizumab, BSC) shows a clear, increasing separation between atezolizumab vs. BSC. [1,33]	Log-logistic extrapolation for both treatment arms Proportional Hazard (PH) assumption considered to be violated at some point in time.	See section 8.3.1.

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated**
Overall survival (OS)	See section 8.3.	See section 8.3.2 and 8.3.3 Exponential extrapolation using trial data from: Nakamichi et al. 2017, Kruser et. al. 2014, IMpower150 trial, Wong et. al., & OAK trial 2016 [36–40]	See section 8.3.2 and 8.3.3 Based on external data due to short follow-up period, OS from various sources: ● Locoregional recurrence: Chemoradiotherapy: Nakamichi et al. 2017 [36] Radiotherapy: Nakamichi et al. 2017 [36] Palliative Treatment: Kruser et. al. 2014 [37] ● 1L Metastatic recurrence: Treatment: IMpower110 trial [41] No Treatment: Wong et. al. 2016 [39] ● 2L Metastatic recurrence: Treatment: OAK trial 2016 [40] No Treatment: Wong et. al. 2016 [39]
Time-to-off treatment (TTOT)	See section 8.5. Based on observed treatment duration in Impower010. No extrapolation required [1,33]	See section 8.5. 8.64 months. Based on observed mean treatment duration in IMpower010. No extrapolation required [1,33]	See section 8.5. IMpower010 trial [1,33]
Modelling of treatment effect	See section 8.3.	Treatment effect starts decreasing at 12 months Treatment effect null at 60 months	Assumption
Modelling of cure proportion	See section 8.3.	Maximum cure proportion 91.5% Cure proportion starts to increase at 24 months Maximum cure proportion reached at 60 months	Maximum Cure proportion: Sonoda et al. 2020 [42] Cure propositions start and stop: Maeda et al. (2010) [43] and assumption
HSUV for DFS	See section 8.4.	On Treatment: 0.76 Off Treatment: 0.76	Data from Jang et al. (2010) [44]

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated**
HSUV for locoregional recurrence	See section 8.4.	Curative treatment: 0.73 Palliative treatment: 0.62	Data from Chouaid et al. (2013) [45] & van den Hout et al. (2006) [46]
HSUV for 1L metastatic health states	See section 8.4.	Treatment: 0.71 No treatment: 0.62	IMpower150 [38] & van den Hout et al. (2006) [46]
HSUV for 2L metastatic health states	See section 8.4.	Treatment: 0.69 No treatment: 0.62	IMpower110 [41] & van den Hout et al. (2006) [46]

Abbreviations: DFS - Disease-free survival; OS - Overall survival; TTOT - Time-to-off treatment; HSUV - Health-state utility values; 1L - First-line; 2L - Second-line; ITC - indirect treatment comparison; ITT – intention-to-treat; PP - per-protocol. * Some of these estimates will be presented in other tables in the document. This table is a summary.

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

Table 8 summarises the patient population as expected in Danish clinical practice, in relation to the trial data, and the cost-effectiveness model.

Patient population in Danish clinical practice:
The patient population in Danish clinical practice is adult patients with stage II-IIIA, Early NSCLC with PD-L1 expression ≥50%, who are EGFR/ALK+ negative. This is in line with the EMA-label.

Patient population in the clinical documentation submitted:
The main documentation submitted is for adult patients with stage II-IIIA, Early NSCLC with PD-L1 expression ≥50%, who are EGFR/ALK+ negative. This subgroup of the IMpower010 trial ITT was used for the clinical documentation [1,33].

Patient population in the health economic analysis submitted:
The patient population characteristics are based on the IMpower010 trial, described above.

Table 8: Patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc.	Used in the model	Danish clinical practice
Age (mean)	61 [1]	61	Unknown, no information available

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc.	Used in the model	Danish clinical practice
Gender (% male)	66.80 % [1]	66.80 %	Unknown, no information available
Weight (kg)	74 [1]	74	Unknown, no information available
Patient population	Main documentation: Adults with stage II-IIIA, early NSCLC with PD-L1 expression ≥ 50%, EGFR/ALK+ negative Supplementary documentation: Adults with stage II-IIIA, early NSCLC with PD-L1+	Adults with stage II-IIIA, early NSCLC with PD-L1 expression ≥ 50%, EGFR/ALK+ negative	Adults with stage II-IIIA, early NSCLC with PD-L1 expression ≥ 50%, EGFR/ALK+ negative

Abbreviations: NSCLC - Non-Small Cell Lung Cancer; PD-L1 - Programmed death-ligand 1; EGFR - Epidermal growth factor receptor; ALK - Anaplastic lymphoma kinase

8.2.2.2 Intervention

Intervention as expected in Danish clinical practice: refer to section 5.3. Inputs regarding atezolizumab in the model are informed by the clinical trial IMpower010 [1,33].

Atezolizumab as monotherapy is approved by the EMA as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with stage II-IIIA NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of TCs and who do not have EGFR mutant or ALK-positive NSCLC.

Atezolizumab can be administered intravenously at a fixed dose of 1.200 mg every 3rd week or as 1680 mg every 4th week until disease progression or unacceptable toxicity [1,33,47].

Based on the IMpower010 study, eligible patients had, following surgical resection, completed up to 4 cycles of adjuvant cisplatin-based chemotherapy (21-day cycles). In IMpower010, atezolizumab is administered as 1.200 mg (IV infusion) for up to 16 cycles [1,33] Table 9 summarises the intervention as used in the clinical trial, cost-effectiveness model, and compared to the Danish clinical practice.

Table 9: Intervention

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	1.200 mg (IV infusion) every 3rd week [1,33,47]	1.200 mg (IV infusion) every 3rd week	1.200 mg (IV infusion) every 3rd week [47] or 1680 mg (IV infusion) every 4th week

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Length of treatment	Up to 16 cycles [1,33]	Same as clinical documentation	Same as clinical documentation

Abbreviations: IV - Intravenous.

8.2.2.3 Comparators

BSC (no treatment). Please see section 5.2.3.

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes in the submitted clinical documentation: The relative efficacy outcomes are summarised in section 7. A head to head trial is available for atezolizumab vs. BSC and relative efficacy outcomes for DFS as well as safety have been estimated directly from IMpower010 [33]. For the remaining outcomes, external evidence has been applied. For more information on model outcomes used in the cost-effectiveness model, see section 8.3.

Relevance of the documentation for Danish clinical practice: The clinical documentation is relevant to the Danish population as it presents efficacy results for the proposed treatment in Denmark using relevant efficacy measures (refer to section 7.2).

The relative efficacy outcomes in the submitted health economic analysis: The key efficacy inputs in the model are DFS and OS. DFS is derived from a direct comparison (atezolizumab vs. BSC) from the IMpower010 study and OS is derived primarily from indirect sources as a function of progression and the specific subsequent treatment regimens (refer to section 8.3). The economic analysis uses the modelled efficacy results (DFS curves) presented in section 8.3.1 and transition probabilities presented in section 8.3.2.

Table 10: Summary of relative efficacy outcome values

Clinical efficacy outcome	Clinical documentation	Values used in the model
DFS	IMpower010 derived survival curve [1,33]	Refer to Table 7
OS	Various sources. See section 8.3	Refer to Table 7

Abbreviations: DFS – disease-free survival; OS – overall survival.

Table 11: Summary of text regarding relevance

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
DFS	See section 7. IMpower010 trial [1,33]	Very relevant, traditionally used in evaluations of drugs used in an adjuvant setting to measure disease status	Very relevant, traditionally used in evaluations of drugs used in an adjuvant setting to measure disease status

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
OS	See section 8.3.	Very relevant, traditionally used in evaluations of drugs in oncology	Very relevant, traditionally used in evaluations of drugs in oncology

Abbreviations: DFS – disease-free survival; OS – overall survival.

8.2.2.5 Adverse reaction outcomes

Adverse reaction outcomes in the health economic analysis are considered for patients in the health state of DFS for the subgroup of the safety population of patients with PD-L1 ≥50%, Stage II-IIIA, without EGFR/ALK+ in the atezolizumab arm, and for both treatment arms in the health states of locoregional recurrence, 1L, and 2L metastatic recurrence in both arms.

Data on AEs are informed by the IMpower010 study for AEs related to DFS state in the atezolizumab arm [1,33]. For an overview of the AEs in the IMpower010 study please see section 7.1.2 and Table 12. External sources were used for evidence on the AE for patients in the health state with locoregional recurrence and 1L and 2L metastatic recurrence. The IMpower010 study did not collect this information. Consequently, AEs for patients in the health state of locoregional recurrence was sourced from the PACIFIC study [48]. For patients in the health states of 1L and 2L metastatic recurrence, AEs were informed by the OAK study [40].

All AEs included in the model are categorised treatment-related grade 3 and above AEs. This inclusion criterion was considered appropriate and sufficient to capture AEs that would impact patients with any consistency; this is to maintain validity in a real-world setting where AEs are monitored in a less strict manner compared with a clinical trial setting.

In the model, AEs affect cost and utilities of patients receiving treatment. Cost of AE management in the DFS health state for atezolizumab is applied in the first cycle for simplicity. Given that all AEs are expected to occur within the first year, i.e., discounting will not apply, this approach is not expected to have any impact on the result. AEs for the remaining health states are applied through the entire time horizon through the health state treatment tunnels in the model for each comparator arm.

Table 12: % of patients with AE, IMpower010 DFS used in the health economic model

AE	Occurrence	% Patients with AE [1,33]
Alanine aminotransferase increased	0	0,00%
Aspartate aminotransferase increased	0	0,00%
Asthenia	1	0,96%
Axonal neuropathy	0	0,00%
Colitis	1	0,96%
Demyelinating polyneuropathy	1	0,96%
Diarrhoea	0	0,00%

Drug eruption	0	0,00%
Drug-induced liver injury	1	0,96%
Dyspepsia	0	0,00%
Encephalitis	1	0,96%
Gait disturbance	0	0,00%
Gastritis	0	0,00%
Genital rash	1	0,96%
Hepatic function abnormal	2	1,92%
Hyperglycaemia	0	0,00%
Hypersensitivity	1	0,96%
Hyponatraemia	0	0,00%
Immune-mediated adverse reaction	0	0,00%
Inappropriate antidiuretic hormone secretion	1	0,96%
Interstitial lung disease	1	0,96%
Leukopenia	1	0,96%
Meningitis	1	0,96%
Multiple organ dysfunction syndrome	0	0,00%
Myalgia	0	0,00%
Myocarditis	0	0,00%
Neuropathy peripheral	0	0,00%
Neutropenia	1	0,96%
Parapsoriasis	1	0,96%
Platelet count decreased	0	0,00%
Pneumonia	0	0,00%
Pneumonitis	1	0,96%
Pyrexia	1	0,96%
Rash	1	0,96%
Rash maculo-papular	0	0,00%
Sarcoidosis	1	0,96%
Secondary adrenocortical insufficiency	0	0,00%
Septic shock	0	0,00%
Thrombocytopenia	1	0,96%
Vomiting	0	0,00%

Abbreviations: AE – Adverse event; DFS – disease-free survival.

8.3 Extrapolation of relative efficacy

8.3.1 Disease-free survival

8.3.1.1 Parametric extrapolation

Patients remain in the DFS health state while they remain disease free and alive as defined by IMpower010. Since the median follow-up of the trial was only 32 months at the latest data cut-off (21 January, 2021), the analysis extrapolates DFS with data from IMpower010 to observe it beyond time points available in the study [1,33].

The analysis fits seven parametric distributions to the data to extrapolate DFS beyond the observed time-period (Exponential, Weibull, Log-Logistic, Log-Normal, Gompertz, Generalized Gamma and Gamma). The analysis separately fits the parametric distributions to the atezolizumab and BSC arms of the trial as the proportional hazard's assumption does not seem to hold.

The proportional hazards assumption requires, in this case, that the hazards of a DFS event are proportional over time across the atezolizumab and BSC arms. However, the log-cumulative hazard plot (Figure 8) shows that the curves do not appear to be parallel, presenting with initial separation and then convergence over time [49].

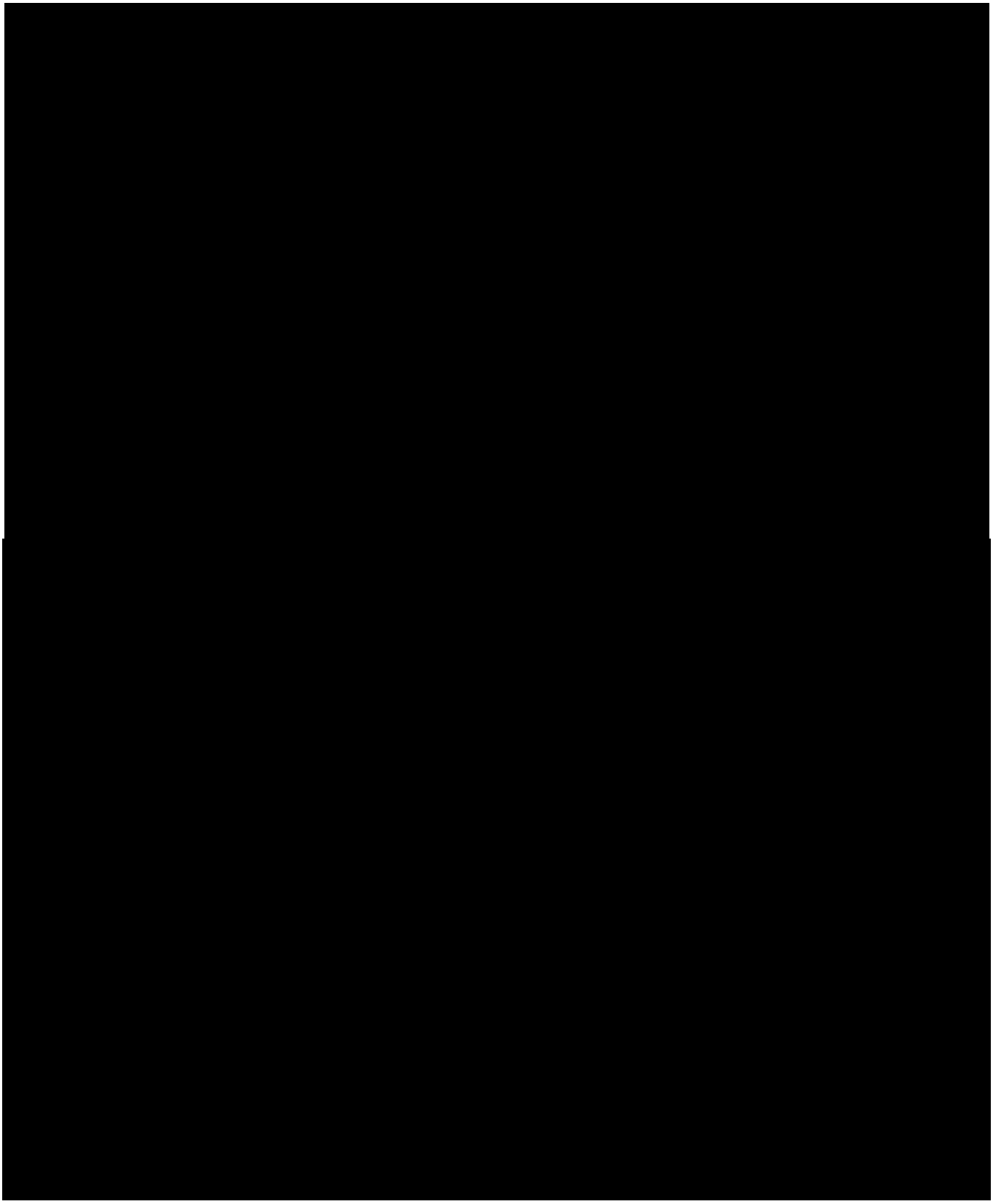
Abbreviations: ATZ - atezolizumab; BSC - best supportive care; DFS – disease-free survival; PD-L1 - programmed death-ligand 1.

The choice of parametric distributions was assessed for their goodness of fit to the data using:

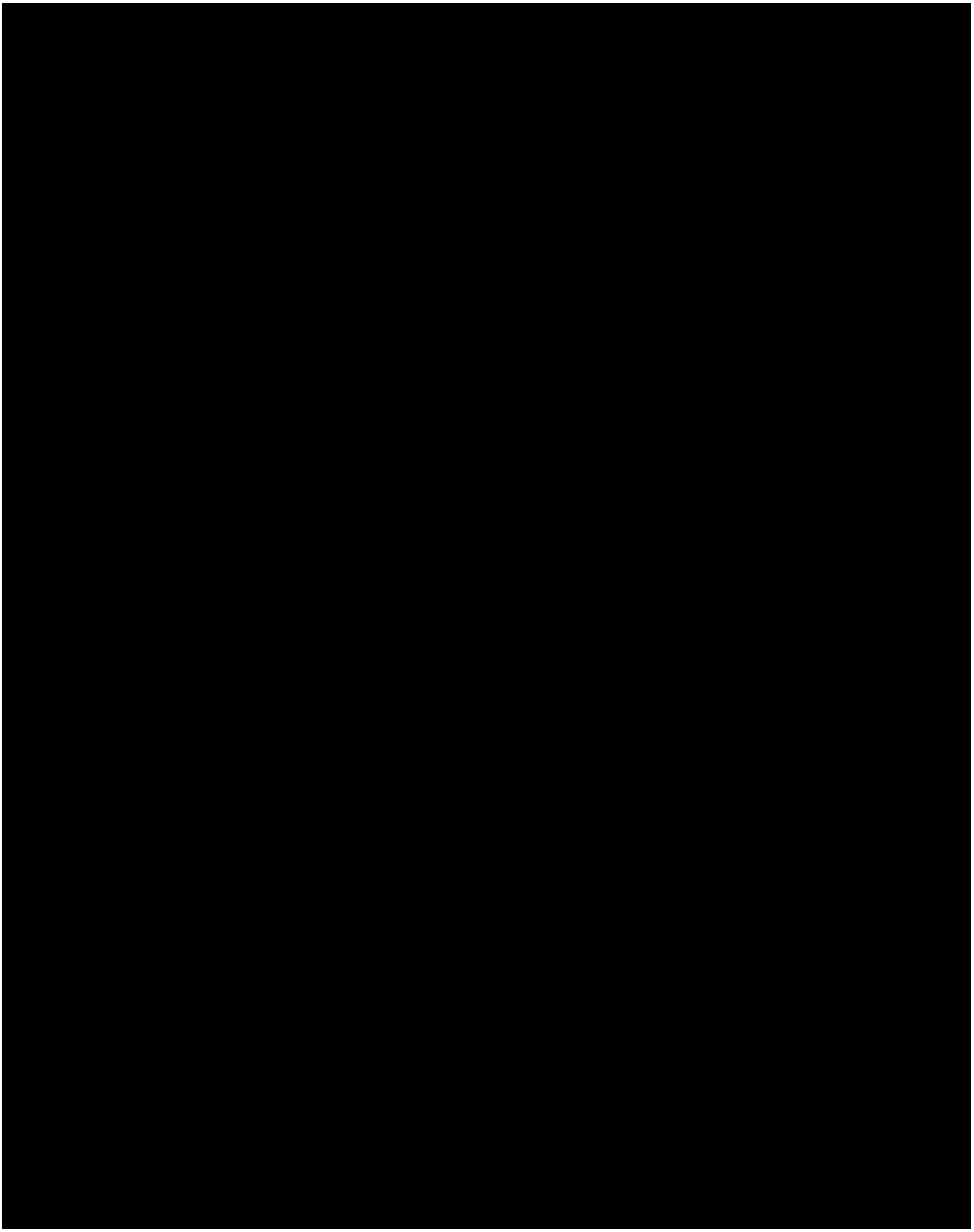
1. The Akaike Information Criterion (AIC). Low values for AIC indicate a better statistical fit of the parametric function to the actual data.
2. The Bayesian Information Criterion (BIC). Low values for BIC indicate a better statistical fit of the parametric function to the actual data.
3. Graphical assessment of each parametric function including hazard behaviour over time (visual inspection), see Appendix G Extrapolation 12.1.

4. Knowledge of the expected extrapolation of DFS times (compared to historical evidence).

Table 13 shows that the performance of the different distributions depends on whether we use the AIC or BIC and that it differs across the different arms. However, a high degree of censoring occurred since a significant proportion of the DFS events did not occur within the follow-up period, i.e., 65% and 47% of the patients in the atezolizumab- and BSC arm, respectively, were still in the DFS health state at maximum follow-up. This fact, combined with the observation that all curves seem to be fitting the observed data rather well, indicates that less emphasis should be put on the statistical fit of the curves and instead the clinical plausibility of the long-term extrapolations should be used to inform the curve selections. Additionally, Figure 9 and Figure 10 appear to show that the accuracy of the parametric distribution in representing the observed data may be comparable.



Abbreviations: BSC – best supportive care; DFS – disease-free survival; PD-L1 - programmed death-ligand 1.



[redacted]

8.3.1.2 Adjustment of DFS

It is critical in the context of extrapolation of DFS data from IMpower010, where trial data with a limited follow-up needs to be extrapolated to a life-time horizon (39 years in the base case), to estimate how long patients treated with atezolizumab will continue being disease-free. The extrapolation of trial data is in line with the DMC method guidelines and is highly relevant to the decision problem in order to account for both the efficacy and cost of the interventions [34].

The model applies three adjustments to the extrapolated DFS to ensure that it predicts proportions of patients in this health state over time that reflect reality.
Figure 13 and Figure 14 presents the curves for the atezolizumab and BSC arms with/without these adjustments for the log-logistic model. The figures show that without these adjustments, the proportion of patients in DFS would be lower.

Cure Adjustment: the model uses IMpower010 data for a time-period where recurrences occur more frequently to extrapolate DFS given the short follow-up. This could lead to the model overestimating the proportion of patients who have recurrence for time points beyond the trial. Therefore, the model allows the proportion of patients who are not at risk of a DFS event to linearly increase from year 2 and reach a maximum of 91.5% at year 5 to prevent this from occurring [1,33]. Evidence shows that most recurrences occur within 5 years. Maeda et al. (2010) show that the recurrence-free probability at 5 years from the point of 5 years after primary tumour resection may vary between ~65-93% and depend on several factors but did not analyse this separately in patients who received adjuvant chemotherapy [43]. Sonoda et al. (2020) show that 6% and 2.5% of recurrences occur at 5-10 years and 10+ years in a sample of patients who underwent curative resection and systematic lymph node dissection [42]. Based on these findings, the maximum cure proportion can be assumed to be 100%. When substracting patients with late (6%) and ultra-late recurrence (2.5%), this results in a proportion of 91.5% applied in the model.

While these studies did not separately study these statistics for the first 2 years after treatment initiation, therapeutic area experts (TAE) from UK confirmed that the proportion of patients who may not be at risk of

[1] Figure 33 is the logit of the survival plot and can assess the fit of the log-logistic model to model DFS where an approximate straight line would indicate good fit. Figure 34 is the inverse of the complement survival plot that can assess the fit of the log-normal model to model DFS where an approximate straight line would indicate good fit.

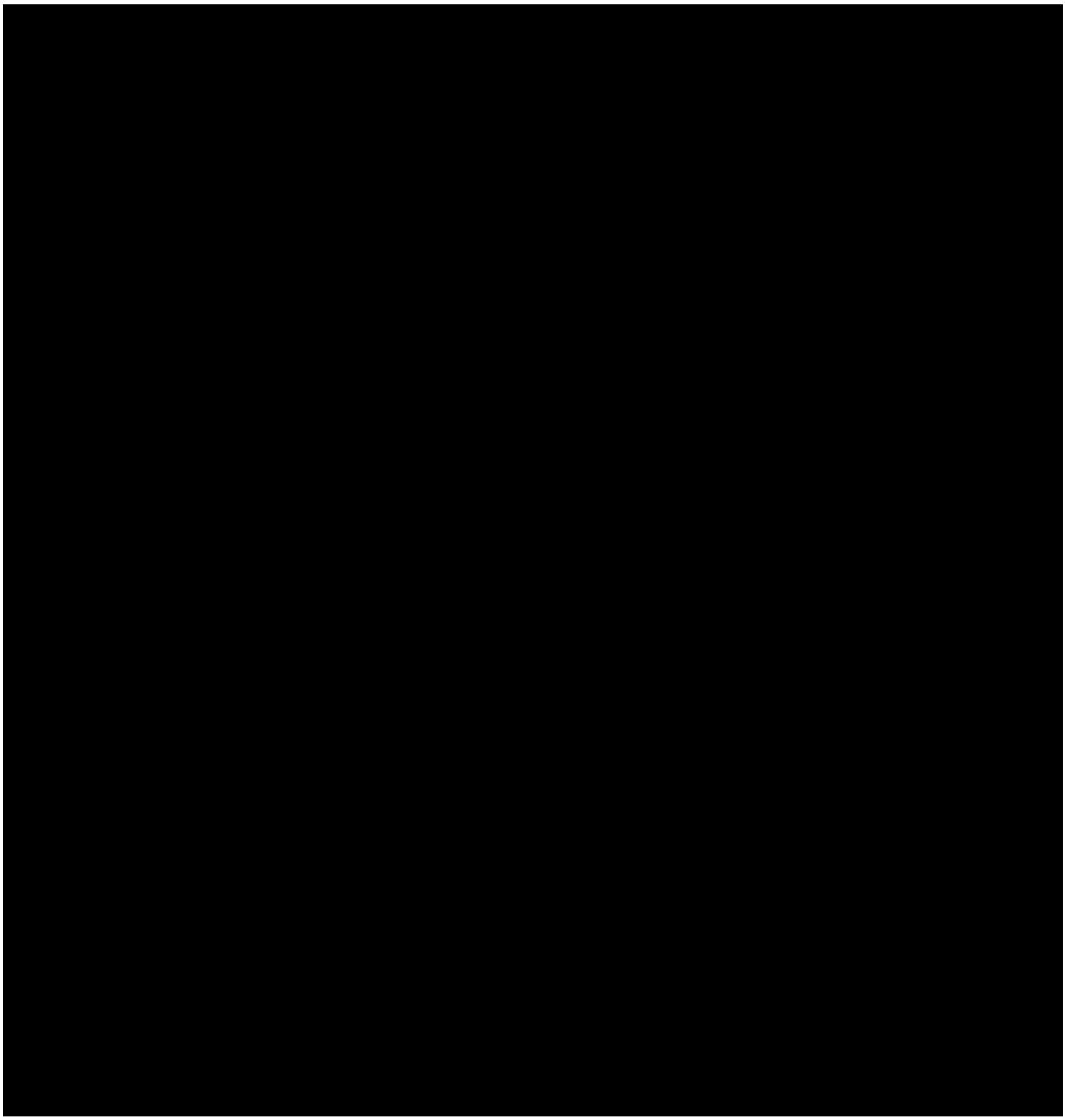
recurrence could start to increase from year 2. Considering no data is available on the time patients start being assumed cured after adjuvant treatment, the cure values in the model (cure_low & cure_high) are based on feedback from TAE in the UK. These experts were consulted during the development and validation of the model. As no available evidence assesses the number of relapses at the time of 2 years after treatment initiation, TAEs confirmed that patients who had not experienced a relapse after two years could be assumed out of risk of relapse. Consequently, it is assumed that the proportion of cured patients increases from year 2 to year 5.

Mortality Adjustment: the model calculates the probability of death in each cycle with IMpower010 data on the number of patients who had death as a first event and median follow-up of patients [1,33]. Patients in the model who are not considered cured confront this probability of death. However, the probability is time-invariant which leads to a point in the cycle at which its value is smaller than the probability of death in the general population. The model does not allow the probability of an uncured patient dying to be smaller than that of an individual from the general population.

Patients in the model who are considered cured are not at risk of cancer related death and only confront a probability of death equal to that which an individual from the general population faces. However, the model allows these probabilities to be adjusted with a standardised mortality ratio to account for excess mortality faced by these patients [50,51]. The standardised mortality ratio is set to 1.25 (25% more cases of death than in the population). Janssen-Heijnen et al. (2012) report a 10 year conditional relative survival of 69-82% with a sample of stage I-III patients and show that it depends on stage and age at diagnosis [50].

Treatment Effect: the model allows the treatment effect of atezolizumab to decrease over time. The probability of a patient in the atezolizumab arm experiencing an event equals the probability of a patient in the BSC arm experiencing an event if the model allows this to occur.

There is currently a lack of data from IMpower010 and external evidence to inform at what time point the treatment effect of atezolizumab ceases [1,33]. Thus, the model assumes that it ceases at year 5 or the same year at which the proportion of cured patients reaches its maximum.



8.3.2 Types of Disease Recurrence

The model calculates the probability of a DFS event in each cycle with the following formula:

$$Event\ Probability\ (t) = \frac{Proportion\ of\ Patients\ in\ DFS_{Distribution,t}}{Proportion\ of\ Patients\ in\ DFS_{Distribution,t-1}}$$

The model first accounts for the patients who die (i.e., event probability – probability of patients who die), and then assigns the remainder of the event probability as locoregional and metastatic recurrences. It uses IMpower010 to calculate the proportion of patients who have either locoregional or metastatic recurrence as a first event [1,33]. Table 14 shows the proportion of patients who had each type of recurrence and death.

The model assigns 61.9% and 38.1% of recurrences as locoregional and metastatic recurrences for the atezolizumab arm and 35.0% and 65.0% as locoregional and metastatic recurrences for BSC arms in the model. It assumes that these proportions will remain the same until the end of the model's time horizon. Although this may not be clinically plausible, this assumption is made as the IMpower010 data is too immature to analyse how the proportion of recurrences evolve.

[redacted]

8.3.2.1 Locoregional Recurrence

Patients who have locoregional recurrence can either be treated with curative intent, palliative intent or not be treated where the model allows this separation to account for patients who cannot or choose not to be treated. Sonoda et al. (2020) report that from their sample of stage IA-IIIB NSCLC patients who underwent curative resection and had locoregional recurrence, 18% received BSC [42]. In a similar group of patients, Wong et al. (2016) report a similar proportion of patients on BSC, 20.5%, as do Brooks et al. (2018), 20% and 10% for local and regional recurrences [39,52]. However, two Danish clinical experts reported a patient split by treatment intent to be 95% for curative treatment and 5% for palliative treatment [53]. Based on the clinical expert statements, we assume the following patient split by treatment intent:

1. Curative treatment: 95% [53]
2. Palliative treatment: 5% [53]
3. No treatment: 0%

Curative Treatment

Patients who receive curative treatment remain in this health state while they are alive and progression-free (PFS). The model allows patients to receive chemotherapy and/or radiotherapy (mono- or combined therapy), and the duration of treatment depends on the chosen regimen which is capped at a maximum of 6 months.

Evidence from the literature on the PFS of patients who had locoregional recurrence after treatment for early NSCLC has been sourced to calculate the probabilities of transitioning to the 1L metastatic recurrence and death health states. This is because IMpower010 does not collect the information necessary to calculate these probabilities.

Thus, the model uses evidence from Nakamichi et al. (2017) to calculate the transition probabilities [36]. This study analyses the PFS and OS of 74 patients who experienced locoregional recurrence after surgery for stages I-III NSCLC, and who were treated with chemoradiotherapy or radiotherapy - median PFS was 19 and 10 months. Figure 15 presents the Kaplan-Meier plot from Nakamichi et al. (2017).

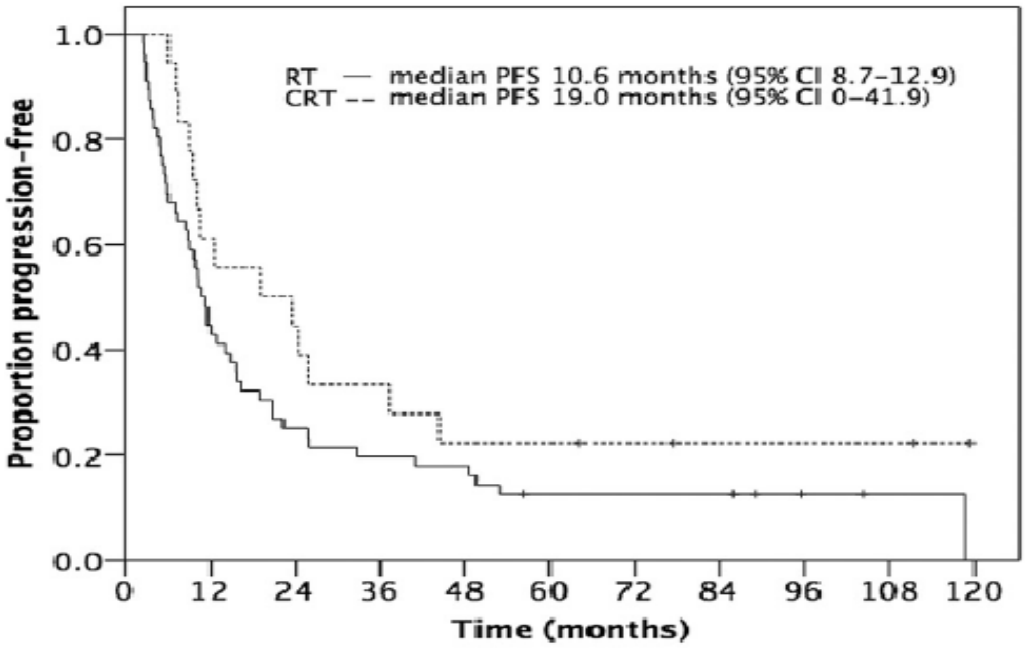


Figure 15: Kaplan-Meier Plot – PFS [36]

Abbreviations: CI – confidence interval; CRT – chemoradiotherapy; PFS – progression-free survival; RT– radiotherapy.

The data from the digitised Kaplan-Meier Plot is analysed with a parametric survival model (exponential) using the algorithm from Guyot, Ades, Ouwens and Welton (2012) [54]. The model uses the results to calculate the monthly transition probability of progressing from locoregional recurrence to metastatic recurrence or death. The probability equals 0.018 and 0.034 if the model assumes all locoregional recurrences are treated with chemoradiotherapy and radiotherapy alone. The model assumes that 77% and 23% of patients who have a progression-free event transition to the 1L metastatic recurrence and death health states. These proportions come from the PACIFIC study [48].

The model switches to calculating the proportion of patients who die with the use of these latter statistics when the proportion of patients who die is smaller than what it would equal if the model used age-adjusted probability of death from the general population.

Palliative Treatment/No Treatment

Patients who receive palliative treatment or no treatment remain in this health state while they are alive. The model allows patients to receive chemotherapy and/or radiotherapy (mono- or combined therapy), and the duration of treatment depends on the chosen regimen which is capped at a maximum of 6 months. The model must source evidence from the literature on the OS of patients who had locoregional recurrence after treatment for early NSCLC to calculate the probabilities of transitioning to the death health state. This is because IMpower010 has not yet collected the information necessary to calculate this probability.

Therefore, the model sources evidence from Kruser et al. (2014) to calculate the transition probability [37]. The study analyses the OS of 37 patients who had locoregional recurrence after radiotherapy for stages I-IV NSCLC, and who were re-treated with either palliative or curative radiotherapy – the median OS for all patients was 5.1 months. Figure 16 presents the Kaplan-Meier plot.

The data from the digitised Kaplan-Meier Plot is analysed with a parametric survival model (exponential). The model uses the results of the analysis to calculate the monthly transition probability of progression from locoregional recurrence to death. The probability equals 0.079, which is greater than those above. The model switches to calculating the proportion of patients who die with the use of these latter statistics when the proportion of patients who die is smaller than what it would equal if the model used age-adjusted probability of death from the general population.

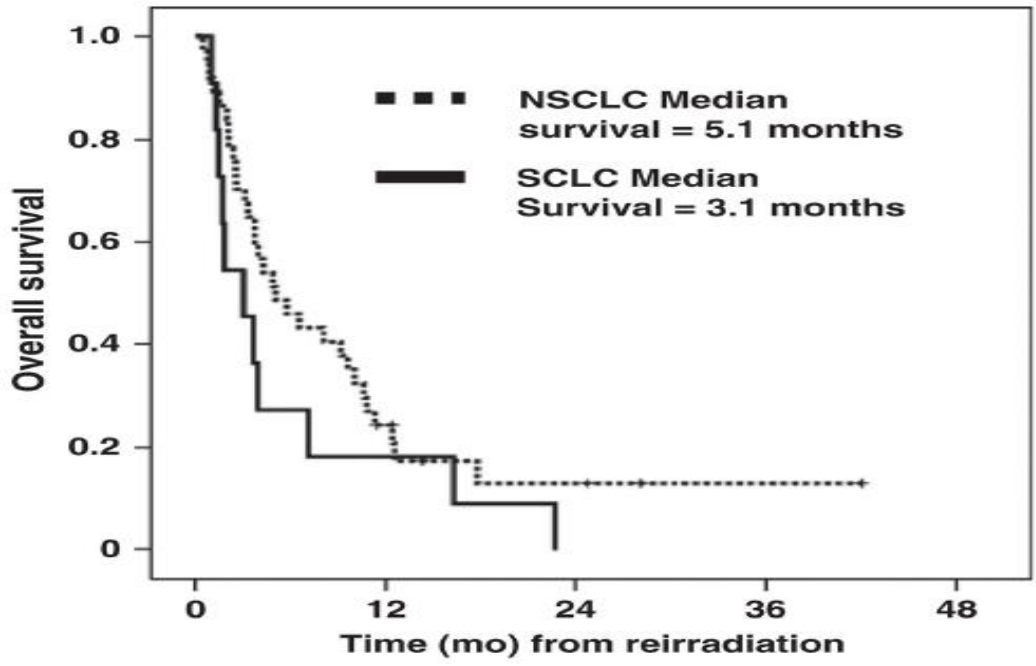


Figure 16: Kaplan Meier – OS [37]

Abbreviations: mo – months; OS – overall survival; NSCLC – non-small cell lung cancer; SCLC – small cell lung cancer.

8.3.2.2 1L Metastatic Recurrence

Patients with metastatic recurrence can be treated with 1L treatment or not be treated. Wong et al. (2016) [39] and Sonoda et al. (2020) report that 22.7% and 18.9% of patients with stage I-III NSCLC who underwent curative treatment received BSC after distant recurrence [42]. Based on this literature and statements from Danish clinical expert that

states that 75% of patients will receive active treatment, it is assumed that the following distribution applies to account for the fact that some patients cannot or choose not to be treated:

1. Treatment: 75%
2. No treatment: 25%

The two Danish clinical experts stated that in the population receiving active treatment, 75% of patients will receive immunotherapy and 25% chemotherapy [55]. Danish Lung Cancer Group (DLCG) guidelines recommend that either immunotherapy or a combination chemotherapy typically consisting of carboplatin and vinorelbine should be used. The Danish clinical experts' testimonies are consequently in line with the treatment guidelines. The two experts stated that patients should receive immunotherapy or a combination of chemotherapy consisting of cisplatin and vinorelbine. Consequently, we assume that 75% of the patients in the model receiving active 1L treatment will receive pembrolizumab and 25% cisplatin and vinorelbine.

Treatment
Patients who receive treatment remain in this health state while they are alive and progression-free.

Based on statements from Danish clinical experts, patients in both the atezolizumab and BSC arm will receive immunotherapy or chemotherapy for 1L metastatic recurrence [53,55]. This is in line with Danish clinical guidelines for NSCLC, where patients are recommended to receive pembrolizumab immunotherapy as 1L metastatic treatment [25,56]. The model caps the duration of treatment to 24 months to reflect the recommendation of clinical guidelines on the use of innovative immunotherapies [57].

The Danish clinical experts consulted, states that patients can be rechallenged with immunotherapy if patients progress later than 12 months after treatment cessation of previous immunotherapy treatment [55]. Consequently, rechallenge with immunotherapy is assumed for patients in the atezolizumab arm in 1L metastatic health state.

To calculate the probabilities of transitioning to 2L metastatic treatment and death health states, evidence on the PFS and OS of patients who had metastatic recurrence after treatment for early NSCLC are estimated from other sources. This is because IMpower010 does not collect all the information necessary to calculate these probabilities. Thus, the model sources data from IMpower110. This study compared the effect of atezolizumab monotherapy to cisplatin/carboplatin and pemetrexed/gemcitabine in patients with stage IV non-squamous or squamous NSCLC that reflects Danish clinical practice [41]. It additionally sources data from IMpower150. This study compared the effect of atezolizumab in combination with carboplatin and paclitaxel with or without bevacizumab to carboplatin, paclitaxel and bevacizumab in patients with stage IV non-squamous NSCLC [38].

The analysis uses data from these studies to run two separate parametric survival models separately for each of the trial arms and assumes that PFS follows exponential distribution. Specifically, it uses the ITT, wild type, PD-L1 high (expression ≥50% of cancer cells) from the IMpower110 study and the ITT, wild type, PD-L1+, B and C arm patients from the IMpower150 study. This allows the model to calculate the monthly probability of having a PFS event (disease progression or death). The model uses the latter transition probability when it does not consider 2L metastatic treatment as an option. Table 15 summarises the probabilities.

[redacted]

The model assumes that patients on immunotherapy and chemotherapy irrespective of drug received, confront the transition probabilities calculated with the use of atezolizumab and chemotherapy arms. The model applies the following probabilities for transitioning to 2L metastatic recurrence for the atezolizumab arm and the BSC arm:

1. Weighted average transition probability atezolizumab arm: 0.07
2. Weighted average transition probability BSC arm: 0.07

The model allows 2L metastatic treatment and assumes that 79% and 21% of all PFS events lead to disease progression or death. These proportions come from IMpower150 – data-cut 15 September, 2017, pooled across three study cohorts [38]. The model allows patients to transition from 1L metastatic treatment to 2L metastatic treatment in the base case. The model uses the transition probabilities estimated with the use of the IMpower110 study in the base-case. While the user can choose to consider either the transition probabilities that the model calculates with the IMpower110 or IMpower150 survival analysis results, the impact on the model's results should be small, as the probabilities appear quite comparable. This is despite differences in the mix of patients in the trials.
The model switches to calculating the proportion of patients who die with the use of these latter statistics when the proportion of patients who die is smaller than what it would equal if the model used age-adjusted probability of death from the general.

No Treatment
Patients not receiving treatment remain in this health state while alive and can only transition to death. OS evidence of patients who had metastatic recurrence after treatment for early NSCLC are sourced from the literature to calculate the probabilities of transitioning to the death health state. This is because IMpower010 does not collect the information necessary to calculate this probability. Thus, the model uses evidence from Wong et al. (2016) to calculate the transition probability of death for patients who had metastatic recurrence after surgery for stages I-III NSCLC – median OS is 3 months for patients on no treatment [39]. Figure 17 presents the Kaplan-Meier plot.

The data from the digitised Kaplan-Meier Plot is analysed with a parametric survival model (exponential). The model uses the results of the analysis to calculate the monthly transition probability of progression from 1L metastatic recurrence to death. The probability equals 0.109, which is greater than those above. When the proportion of patients who die is smaller than what it would equal if the model used age-adjusted probability of death from the general population, the model switches to calculating the proportion of patients who die with the use of the latter.

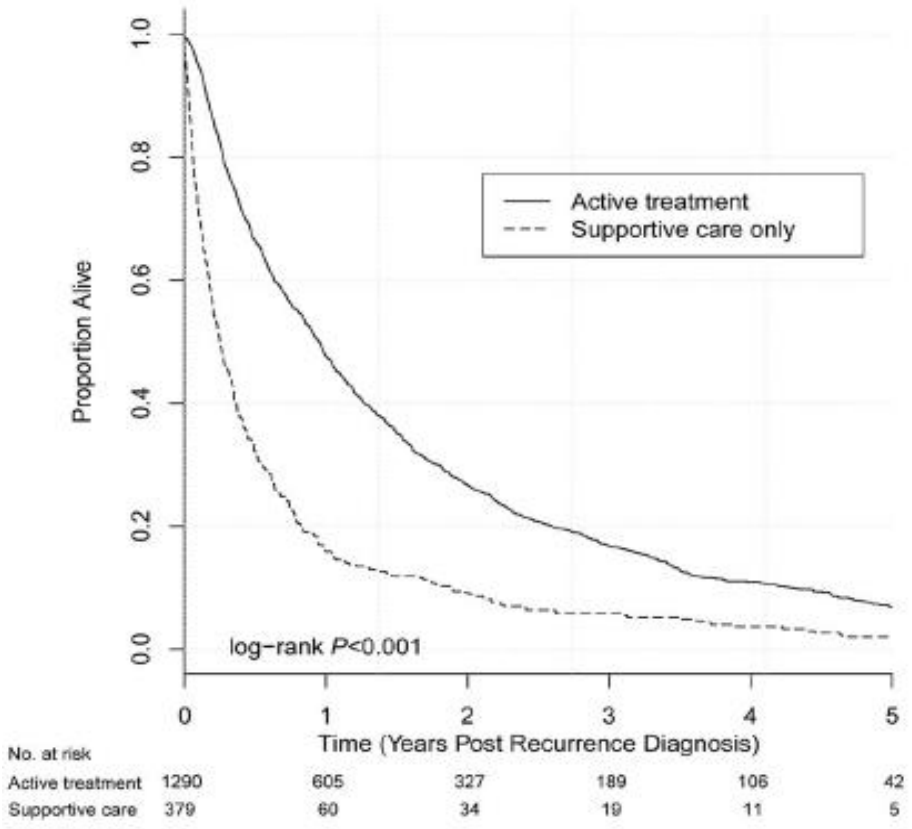


Figure 17: Kaplan Meier – OS [39]

Abbreviation: OS – overall survival.

8.3.2.3 2L Metastatic Recurrence

Patients can be treated or not treated after metastatic progression as evidence shows that not all patients proceed to 2L metastatic treatment after this occurs [41,58]. Danish clinicians noted that the proportion of patients who proceed to later lines of treatment depends on their efficacy as well as of treatments in the 1L suggesting that it may fluctuate over time [53]. For the base-case the following proportions are assumed:

1. Treatment: 45% [53]
2. No treatment: 55% [53]

Treatment

Patients who receive treatment remain in this health state while they are alive and from there, they can only transition to the death health state. To calculate the monthly probabilities of transitioning to death, evidence from other sources on the OS of patients with progression of metastatic recurrence after treatment for early NSCLC are used. This is because IMpower010 does not collect the information necessary to calculate these probabilities.

Therefore, the model sources evidence from the OAK study. This trial compared the effect of atezolizumab to docetaxel in patients with locally advanced or metastatic NSCLC who had failed platinum containing therapy [40].

The analysis uses data from the trial to run two parametric survival models separately for each trial arm and assumes that OS has an exponential distribution. This allows the model to calculate the monthly probability of transitioning to death. Table 16 presents these transition probabilities.

Table 16: Transition Probabilities (2L metastatic treatment to death)

The clinical guidelines state that rechallenging with 1L therapy can be considered, if patients had good response to the primary treatment and a long period without treatment (>12 months) [25]. However, patients in the 2L state progress much sooner than 12 months after previous immunotherapy, and consequently no rechallenging with immunotherapy is assumed in the 2L metastatic health state. The DLCG guidelines recommend single-agent chemotherapy in the 2L metastatic health state [25]. It is therefore assumed that all patients eligible for active treatment 2L metastatic recurrence state will receive chemotherapy (docetaxel).

The following transition probabilities are therefore applied in the model:

1. Atezolizumab arm: 0.07
2. BSC arm: 0.07

The model switches to calculating the proportion of patients who die with the use of these latter statistics when the proportion of patients who die is smaller than what it would equal if the model used age-adjusted probability of death from the general population (see section Overall Survival for more details on implementation).

No Treatment

Patients who receive no treatment remain in this health state while they are alive and from there, they can only transition to the death health state. As IMpower010 does not collect the information necessary to calculate these probabilities, the same source and method to model the OS of these patients is used as the approach used to model the overall survival of patients who are in the 1L metastatic recurrence health state (refer to 1L Metastatic Recurrence for details and result).

8.3.3 Overall Survival

The model switches to the use of age-adjusted probabilities of death from the general population to calculate the proportion of patients who transition to death when they are greater than the probabilities that it estimates with the use of the literature or trial data [59]. This is irrespective of the health state. The formula below presents this where *A* and *B* equal the health state specific death probability and age-adjusted general population death probability:

$$Death\ Probability_{(health\ state,treatment\ status)} = \begin{cases} A_{(health\ state,treatment\ status)}, & A_{(health\ state,treatment\ status)} \leq B_{(general\ population)} \\ B_{(general\ population)}, & A_{(health\ state,treatment\ status)} > B_{(general\ population)} \end{cases}$$

This adjustment forces the model to not apply a probability of death that is lower than the one observed in the general population in Denmark, as this would be implausible in reality.

Figure 18 shows the modelled probability of death, where the adjustment with mortality rates from the general population can be observed by the stepwise form of the graphs. Figure 19 shows the impact the adjustment has on the modelled survival estimates.

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Utility inputs

The model incorporates health related quality of life via utility values – 0 = death and 1 = perfect health. It sets a unique value to each health state and treatment intent that alive patients realise in each cycle.

IMpower010 does not collect patient reported outcomes, therefore the model sources information on health state utility values from the literature and other trials. The decision on which studies to source this information from can be arduous given that differences in the sample of patients and methodological approach used can lead to the estimation of considerably different utility values across studies. As the utilities were derived from external sources with no access to IPD, mapping to Danish EQ-5D-5L tariffs is not possible. Therefore, the model allows the choice of health state utility values (EQ-5D-3L) to come from a selection of studies.

8.4.1.1 Disease-Free Survival

A SLR identified 25 studies that provide health related quality of life values for patients treating early NSCLC. Table 17 provides information on the reason why the model excludes certain studies from the analysis. We can see from the table that the model only considers the evidence that come from five out of the 25 studies – Manser et al. (2006), Grutters et al. (2010), Jang et al. (2010), Black, Keeler and Soneji (2014), Yang et al. (2014).

Table 17: Exclusion of studies (Health Related Quality of Life SLR)

Criteria	Number of Studies
Combine patients with NSCLC and SCLC	3
Do not specifically show values for stage II-IIIA (e.g. combine stage II-IIIA patients with stage I or IV)	14
Do not consider patients who did not receive surgery (e.g. received radiotherapy for inoperable NSCLC)	2
Follow-up time period after resection too short	1

Abbreviations: NSCLC - non-small cell lung cancer; SCLC – small cell lung cancer.

The model includes DFS utility estimates from Manser et al. (2006), Grutters et al. (2010), Jang et al. (2010), Black, Keeler and Soneji (2014), Yang et al. (2014) [44,60–63]. While some of the five studies also report utility values for populations who are not of interest, the model only considers the values obtained from the population of interest (Table 18 summarises these values).

Table 18: Utility values from studies considered

Study	Population	Utility value
Manser et al. (2006) [61]	Stage II-IIIA, 6 months post-surgery	0.55
Grutters et al. (2010) [62]	Stage II Stage III	0.74 0.70
Jang et al. (2010) [44]	Stage II Stage III	0.78 0.73
Black, Keeler and Soneji. (2014) [63]	Stage II, 12 months post-diagnosis Stage III, 12 months post-diagnosis	0.68 0.71
Yang et al. (2014) [60]	PS 0-4, stage II-III	0.83

While the model considers all these studies, the choice of using evidence from Manser et al. (2006), Grutters et al. (2010) and Black, Keeler and Soneji (2014) could lead to the use of lower utility values for patients in the DFS than in the locoregional recurrence health state, which is clinically not plausible [61–63]. Therefore, the model uses the values from Jang et al. (2010) due to this and because it provides the more conservative values to account for uncertainty that arises due to the use of external sources to define them [44].

The model allows a disutility to be applied to patients in the atezolizumab arm of the model to account for the impact immunotherapy may have on quality of life in addition to surgery plus adjuvant chemotherapy. The calculation is based on the prevalence of grade 3 and above treatment emergent AEs observed in IMpower010 [1,33]. The model assumes that the patients accrue the total disutility of the events in the first cycle of the model. This analysis does not consider the disutility of AEs in the base case despite the availability of this function, as evidence on the frequency of AEs is unlikely to have an important impact on the outcomes.

8.4.1.2 Locoregional Recurrence

For the locoregional recurrence health state, the model uses utility values from Chouaid et al. (2013) for patients who were treated with curative intent [45]. The study is prospective in nature and considers a sample of 319 patients with locally advanced and metastatic NSCLC across 25 centres. Table 19 provides the multivariate regression output on the drivers of health-related utility from the study. Given this output, the quality of life of patients who treat with curative intent in the model equals 0.73 (intercept + 1L progressive disease variables).

Table 19: Multivariate Regression - Utility Values

Variable	Estimate	Standard Error	P-Value

Intercept	0.77	0.03	<0.01
Stage IV	-0.07	0.04	0.029
1L Progression Free	0.00	NA	NA
1L Progressive Disease	-0.04	0.04	0.41
2L Progression Free	0.03	0.04	0.47
2L Progressive Disease	-0.11	0.08	0.18
3/4L Progression Free	-0.10	0.06	0.09
3/4L Progressive Disease	-0.26	0.08	<0.01

Abbreviations: 1L – first-line; 2L – second-line; 3L – third-line; 4L – fourth-line.

The model sources utility values from van den Hout et al. (2006) for patients who treat with palliative intent [46]. The study conducts a cost-utility analysis comparing radiotherapy schedules consisting of 10 fractions of 3Gy versus two fractions of 8Gy in poor prognosis patients with stage IIIa-IV NSCLC (based on Dutch randomised control trial: ISRCTNO4886579). The study calculates a median utility value equal to 0.62 and 0.52 for patients on the 10 and 2 fraction schedules and uses the former value as the utility of these patients may converge to the higher value some weeks after randomization. Patients who do not receive treatment also realise this disutility. For the base-case, the analysis uses utility values from Chouaid et al. (2013) [45].

8.4.1.3 1L Metastatic Recurrence

The model allows for the use of health state utility values estimated with the IMpower110/150 data but also utility values from Chouaid et al. (2013) for patients who receive 1L metastatic treatment are available within the model [38,41,45]. The utility values from the clinical trials come from statistical models that stratified patients by progression. The model also sources utility values from van den Hout et al. (2006) for patients who are not treated [46]. Table 20 provides an overview of the utility values. The utility value from the IMpower110 and 150 is 0.76 and 0.71 respectively. Consequently, the model uses the values from IMpower150 in the base case as the use of IMpower110 would lead to the use of a higher utility value for patients in 1L metastatic recurrence than in the locoregional recurrence health state, which is clinically not plausible.

Table 20: Health State Utility Values – 1L Metastatic Treatment

Treated			Not Treated
Chouaid et al. (2013) [45]*	IMpower150 [38]	IMpower110 [41]	van den Hout et al. (2006) [46]
0.70	0.71	0.76	0.62

*The model uses the parameters *Intercept* and *Stage IV* from Table 19.

8.4.1.4 2L Metastatic Recurrence

The model also sources utility values from Chouaid et al. (2013) [45] for patients who receive 2L metastatic treatment but also allows the use of health state utility values from Nafees et al. (2008) [64] and the values estimated with the IMpower110/150 data. The model uses the values from IMpower110 in the base case.

Table 21: Health State Utility Values – 2L Metastatic Treatment

Treated	Not Treated

Chouaid et al. (2013) * [45]	Nafees et al. (2008) [64]	IMpower150 [38]	IMpower110 [41]	van den Hout et al. (2006) [46]
0.59	0.65	0.69	0.69	0.62

*The model uses the parameters *Intercept*, *Stage IV*, and *Progressive Disease (2L)* from Table 19. Abbreviation: 2L – second-line.

8.4.1.5 Age-adjustment of the utility values

The health states utility values were adjusted to ensure that the HRQoL of the patient cohort at any given age does not exceed the HRQoL of the general Danish background population. The utilities were age-adjusted with a general population multiplier based on Danish age-specific data source from DMC's guidelines 2021 [65].

The health state utility values in the model decrease with more progressed NSCLC. This is in accordance with the opinion of therapeutic area experts from the UK that the quality of life of a patient should generally decrease the more severe their disease. However, the utility values are not time-varying and due to this they may be greater than age-adjusted general population utility values in certain cycles. Therefore, as per Danish guidelines, the HRQoL values have been age-adjusted within the model based on the modelled patient's average age using the multiplicative method [34].

8.5 Resource use and costs

Costs and resource use vary depending on the administered treatment and health states. The model includes direct medical costs, as well as transport costs and time spent on treatment by patients, consistent with the restricted societal perspective as described in the DMC guidelines [34,66].

The following section regarding cost and resource use is presented per health state, containing state-specific information regarding drug acquisition costs, administration costs, follow-up costs and AE costs. Drug costs are sourced from Medicinpriser.dk and applied as pharmacy purchasing prices (AIP). Administration costs, follow-up costs, and AE costs are based on Danish diagnosis related groups (DRG) tariffs from 2022 and labportalen.dk. Patient and transportation costs are based on the DMC catalogue for unit costs and are presented in a separate section covering all patient- and transportation costs for all health states [67].

8.5.1 Disease-free Survival

8.5.1.1 Treatment Cost

Patients who are in the atezolizumab arm of the model, start on treatment in the DFS health state. Its duration is limited to sixteen cycles as per the trial protocol; however, patients may discontinue treatment before this point for reasons other than death and progression. The IMpower010 data shows that of the safety-evaluable population, 67.9% of patients completed the planned 16 cycles of treatment, whereas the remaining patients discontinued it due to AEs, relapse or other reasons [1,33]. For the base-case, drug costs are based on the time-to-off treatment data from IMpower010, as this data considers treatment discontinuations for reasons other than disease progression (Table 22 shows the TTOT data - proportion of patients on atezolizumab in each cycle). The model includes an option to model time on treatment by disease free survival, however, this is not used in the base case analysis, as this only considers treatment discontinuations due to disease progression.

Table 22: TTOT (IMpower010, TTOT, Stage II-III, PD-L1 ≥50%, ATZ arm, data cut 21 Jan 2021)

The default drug cost inputs in the model are based on Danish pharmaceutical purchasing prices (AIP). The cost per vial of atezolizumab is 21.799,09 DKK for the 840 mg vial and 31.141,55 DKK for the 1,200 mg vial [68].

Table 23: Drug vial sizes and costs for Atezolizumab

Drug	Small vial (size)	Small vial (cost)	Large vial (size)	Large vial (cost)	Administration cost
Atezolizumab	840 mg	21,799.09 DKK	1,200 mg	31,141.55 DKK [68].	2,180 DKK [69]

The model uses the information on the proportion of patients who complete each cycle of treatment, the dose size and treatment schedule, and cost of atezolizumab to calculate the monthly cost of treatment.

8.5.1.2 Follow-Up Costs

Patients across the arms of the model receive follow-up healthcare. The current standard of care after surgery plus adjuvant chemotherapy for NSCLC consists of CT chest scans every 3 months for 2 years then every 6 month until year 5 [70]. A unit cost of 2,411 DKK (DRG 30PR06) is applied per CT chest scan. Blood samples are taken 14 days after treatment initiation and thereafter one day prior to each treatment administration. Blood samples tests include Haemoglobin, B-leukocytes, thrombocytes, electrolytes, INR, creatinine, bilirubin, ASAT/ALAT LDH, basic phosphatase, amylase, TSH, T3, and T4. The estimated cost of the blood samples is calculated based on analysis cost catalogue, which results in a unit cost of 550 DKK per blood sample.

Table 24 summarises the unit cost for healthcare resources. Table 25 summarises the utilisation of these healthcare resources. Utilisation of healthcare resources is based on the Danish clinical guidelines for treatment of lung cancer [70]. Assumptions of healthcare resource use have been validated by Danish clinical experts for this application [53]. This results in a monthly healthcare resource use cost of 4,430DKK.

Table 24: Unit costs for other healthcare resources

Health care resource	Costs	Reference, DRG 2022
CT scan	2,411 DKK	DRG gruppe 30PR06, DC349 Kræft i lunge UNS, UXCC75 CT-skanning af lunger [71]
Outpatient visit	2,180 DKK	DRG gruppe 04MA98, DC349 Kræft i lunge UNS, DZ080B Kontrolundersøgelse efter operation af kræft i lunge [72]
Blood samples	550 DKK	Labportal.rh.dk, Hæmoglobin, B-leukocytter, thrombocytter, elektrolytter, INR, kreatinin, bilirubin, ASAT/ALAT LDH, og basisk fosfatase + (immunterapi: TSH + T4 + T3) + Lipase + Amylase [73]

Abbreviations: CT - computed tomography; DKK - Danish Krones; DRG - Diagnose related group

Table 25: Health care resource use while disease-free

Health care resource	Number of units yearly	Reference [6,53,70]
CT scan	2-4 scans	Every 12th week for 2 years, then every 24th week up to 5 years
Outpatient visit	17 times	Every 3rd week
Blood samples	17 times	Every 3rd week [53]

Abbreviation: CT - computed tomography; DKK - Danish Krones

According to the Danish clinical experts consulted, patients will prior to treatment initiation get a bronchoscopy and electrocardiogram (ECG). The cost of a bronchoscopy is estimated to have a unit cost of 1,515 DKK and ECG a unit cost of 2,180 DKK, see Table 26. This cost is included as a one-off cost in the DFS health state as this is conducted before treatment initiation.

Table 26: Resource use and unit cost of ECG and bronchoscopy

Health care resource	Unit	Costs	Reference, DRG 2022
Electrocardiogram	1	2,180 DKK	DRG gruppe 04MA98, DC349 Kræft i lunge UNS, ZZ2688 Monitorering af CTG og elektrokardiogram [74]

Bronchoscopy	1	1,515 DKK	DRG gruppe 23MA04, DZ080W kontrolundersøgelse efter operation, KUGC08 Rigid bronkoskopi med biopsi af lunge [72]

Abbreviations: DKK - Danish Krones; DRG - Diagnose related group

8.5.1.3 AE Management

The model captures the costs associated with the management of treatment-related grade 3 and above AE for the DFS state for the subgroup of the safety population of patients with PD-L1 ≥50%, Stage II-IIIA, without EGFR/ALK+ in the atezolizumab arm. It calculates the cost of AE with information on the occurrence of each event, proportion of patients experiencing them, and their estimated unit cost. See Table 27 for overview of the unit costs for AE management.

Table 27: Unit costs for AE management

AE management	Costs	Reference, DRG 2022 [75]
Asthenia	4,460 DKK	DRG: 23MA03, Diagnosis: DR539A
Colitis	6,756 DKK	DRG: 06MA11, Diagnosis: DK523
Demyelinating polyneuropathy	3,618 DKK	DRG: 01MA98, Diagnosis: DG629
Drug-induced liver injury	2,910 DKK	DRG: 07MA98, Diagnosis: DK716A
Encephalitis	3,168 DKK	DRG: 01MA98, Diagnosis: DA879
Genital rash	2,041 DKK	DRG: 09MA98, Diagnosis: DR219
Hepatic function abnormal	2,910 DKK	DRG: 07MA98, Diagnosis: DR945
Hypersensitivity	3,888 DKK	DRG: 21MA01, Diagnosis: DT887B
Inappropriate antidiuretic hormone secretion	1,954 DKK	DRG: 10MA98, Diagnosis: DE222
Interstitial lung disease	2,180 DKK	DRG: 04MA98 Diagnosis: DJ848
Leukopenia	25,419 DKK	DRG: 16MA10, Diagnosis: DD728H
Meningitis	67,383 DKK	DRG: 01MA03, Diagnosis: DG039
Neutropenia	3,176 DKK	DRG: 16MA98, Diagnosis: DD709

AE management	Costs	Reference, DRG 2022 [75]
Parapsoriasis	2,041 DKK	DRG: 09MA98, Diagnosis: DL419
Pneumonitis	2,180 DKK	DRG: 04MA14, Diagnosis: DJ110
Pyrexia	18,647 DKK	DRG: 18MA04, Diagnosis: DR509
Rash	2,041 DKK	DRG: 09MA98, Diagnosis: DR219
Sarcoidosis	2,180 DKK	DRG: 04MA98, Diagnosis: DD860
Thrombocytopenia	38,408 DKK	DRG: 16MA03, Diagnosis: DD696

Abbreviations: AE – adverse event; DKK - Danish Krones; DRG - Diagnose related groups

8.5.2 Locoregional Recurrence

8.5.2.1 Treatment Cost

The model allows the choice of separate treatment options for curative and palliative treatment. According to Danish guidelines the choice of the treatment options is radiotherapy and chemotherapy. Information regarding radiotherapy and type of chemotherapy drugs, the dose size, and treatment schedule is based on the Danish clinical guidelines to calculate the treatment cost [70].

Table 28 shows the curative and palliative treatment options that can be applied in the model. The model sets chemoradiation therapy as the curative option as evidence shows that the majority of patients who receive radiotherapy for locoregional recurrence/locally advanced cancer also receive chemotherapy. Information on the dose size and treatment schedule were sourced from Danish clinical lung cancer guidelines [76]. The model sets chemotherapy as the palliative treatment option due to evidence showing that it may be more commonly used than other options (radiotherapy cost per fraction set to 2,864 DKK (DRG 27MP04); refer to Table 29 or list of drug vial sizes and costs, and administration costs).

Table 28: Treatment options (curative vs. palliative treatments for locoregional recurrence)

Option	Curative treatment	Palliative treatment
Chemotherapy inclusion		
Drug 1	Cisplatin	Cisplatin
Dose size	75 mg/m^2 [53,77]	75 mg/m^2 [53,77]
Units of cycle	4	4

Option	Curative treatment	Palliative treatment
Doses per cycle	1	1
Weeks between cycles	3	3
Drug 2	Vinorelbine	Vinorelbine
Dose size	30 mg/m^2 [78]	30 mg/m^2 [78]
Units of cycle	4	4
Doses per cycle	1	1
Weeks between cycles	3 [53,77]	3 [53,77]
Radiotherapy inclusion	Yes [76]	Yes [79]
Total dose	50 Gy	30
Dose per fraction	5 Gy	10 Gy
Fractions per week	3	3

Abbreviation: Gy - grays; m^2 - square meter; mg – milligram; N/A - Not applicable. Reference: dcmg.dk [76], clinical experts, promedicin.dk [80]

Table 29: Drug vial sizes and costs for locoregional recurrence

Drug	Small vial (size)	Small vial (cost)	Large vial (size)	Large vial (cost)	Administration cost
Cisplatin	50 mg	100 DKK	1,200 mg	200 DKK [68].	2,180 DKK [69]
Vinorelbine	10 mg	245 DKK	50 mg	1,240 DKK [68].	2,180 DKK [69]

Abbreviation: DKK - Danish Krones; mg – milligram.

8.5.2.2 Follow-up costs

As described for the DFS health state, prior to every treatment initiation patient will get a bronchoscopy (ECG), see Table 26 for the unit costs. This is applied as a one-off cost when entering the locoregional recurrence health state.

Patients who have locoregional recurrence receive follow-up healthcare regardless of curative or palliative status. We assume that patients that are in locoregional recurrence state receive monitoring CT-scans in line with the Danish clinical treatment guidelines. We assume similar healthcare resource use as during the disease-free health state following adjuvant treatment, therefore resource use will be similar to the utilisation presented in Table 25.

8.5.2.3 AE management

The model allows AE management costs to be considered for locoregional recurrence treatment. All AE management costs are summarised in Table 27.

Table 30. AE Ocurrence and Unit Cost of Management

AE	Bi-Weekly Probability of Event	Unit cost DKK	Source
Anaemia	0.002	3,176	DRG-gruppe 16MA98, DD649 Anæmi UNS
Haemoptysis	0.001	2,180	DRG-gruppe 04MA98, DR042 Hæmoptyse
Hypokalaemia	0.003	1,954	DRG-gruppe 10MA98, DE876 Hypokaliæmi
Pneumonia	0.003	2,180	DRG-gruppe 04MA98, DJ189 Pneumoni UNS
Pneumonitis	0.001	2,180	DRG-gruppe 04MA98, DJ129 Viruspneumoni UNS
Radiation Pneumonitis	0.002	2,180	DRG-gruppe 04MA98, DJ700 Strålepneumonitis
Endocrinopathy	0.001	1,954	DRG-gruppe 10MA98, DE349 Endokrin sygdom UNS
Monthly AE management cost			58.86 DKK

Abbreviation: AE – Adverse events, DKK – Danish Krones, DRG - Diagnose related groups
Note: Bi-weekly probability – the probability of an event every second week.

8.5.3 1L/2L Metastatic Recurrence

8.5.3.1 Treatment Costs

The model allows the choice of four separate treatment options for 1L and 2L metastatic treatment. Drug costs for the treatment options are presented in Table 31. The model uses the four treatment options presented in Table 32 to define 1L metastatic treatment.

Table 31: Drug vial sizes and costs for metastatic treatment 1L/2L

Drug	Small vial (size)	Small vial (cost)	Large vial (size)	Large vial (cost) [68]	Administration cost [69]
Pembrolizumab	N/A	N/A	100 mg	23,204.61 DKK	2,180 DKK
Cisplatin	50 mg	100 DKK	1,200 mg	200 DKK	2,180 DKK

Drug	Small vial (size)	Small vial (cost)	Large vial (size)	Large vial (cost) [68]	Administration cost [69]
Carboplatin	150 mg	84 DKK	450 mg	203.00 DKK	2,180 DKK
Vinorelbine	10 mg	245 DKK	50 mg	1,240 DKK	2,180 DKK
Docetaxel	20 mg	71 DKK	160 mg	309.00 DKK	2,180 DKK
Pemetrexed	100 mg	1,133.77 DKK	500 mg	4,724.06 DKK	2,180 DKK
Atezolizumab	840 mg	21,799.09 DKK	1200 mg	31,141.55 DKK	2,180 DKK

Abbreviation: 1L – first-line; 2L – second-line; DKK - Danish Krones; mg – milligram.

Table 32: Treatment options dosing for 1L metastatic treatment

Inputs	Option 1 [53,81]	Option 2 [53,81]	Option 3 [53,81]	Option 4 [53,81]
Drug 1	Pembrolizumab	Cisplatin	Carboplatin	Atezolizumab
Dose size	200 mg	75 mg/m^2 [53,77]	400 mg/m^2	1.200 mg/fixed [81]
Doses per cycle	1	1	1	1
Weeks between cycles	3	3	3	3
Drug 2	N/A	Vinorelbine	Vinorelbine	N/A
Dose size	N/A	30 mg/m2 [78]	30 mg/m2 [78]	N/A
Doses per cycle	N/A	1	1	N/A
Weeks between cycles	N/A	3	3	N/A

Abbreviation: 1L – first-line; kg – kilograms; m^2 - square meter; mg – milligram; N/A, not applicable

The model uses the four treatment options to define the treatment components for 2L metastatic treatment. The four different treatment options for 2L metastatic treatment are presented in Table 33. Based on the Danish treatment guidelines from DLCG and Danish clinical experts' testimonies, it is assumed that patients who have received adjuvant atezolizumab and who are progressing to the 1L and 2L metastatic can be rechallenged with immunotherapy if the progression occurs >12 month after treatment cessation with the previous immunotherapy. Patients in the BSC arm will primarily receive immunotherapy in 1L metastatic recurrence and in 2L metastatic recurrence if the progression occurs >12 month after treatment cessation with the previous immunotherapy. However, as explained in section 8.3.2.3, patients in the 2L metastatic health state arm are progressing within 12 months for both the atezolizumab and

BSC. Consequently, no patients are assumed to receive immunotherapy in 2L metastatic recurrence in the model, and it is assumed that all treatment eligible patients will receive docetaxel.

Table 33: Treatment options dosing for 2L metastatic treatment

Inputs	Option 1	Option 2	Option 3	Option 4
Drug 1	Pembrolizumab	Docetaxel	Cisplatin	Atezolizumab
Drug 2	N/A	N/A	Vinorelbine	N/A

Abbreviation: 2L – second-line; N/A- Not applicable. References: Medicinraadet.dk, Clinical experts.

8.5.3.2 Follow-Up Costs

Patients who have metastatic recurrence receive follow-up healthcare regardless of treatment status. In this regard, the model assumes that patients that are in 1L or 2L receive monitoring CT-scans in line with the Danish clinical treatment guidelines. The model assumes similar healthcare resource use as during the disease-free health state, following adjuvant treatment. Therefore, resource use will be similar to the resource utilisation presented in Table 25. The cost of ECG and bronchoscopy before treatment start is accrued as a one-off cost for all patients, when entering the 1L- and 2L metastatic recurrence health state, see Table 26.

8.5.3.3 AE management

The model allows AE management costs to be considered for 1L and 2L metastatic treatment using data from the OAK study to inform model inputs. All AE management costs are summarised in Table 34.

Table 34: AE occurrence and unit cost of management (OAK)

AE	Weekly Probability of Event - Intervention Arm (Atezolizumab)	Weekly Probability of Event - Control Arm (Docetaxel)	Unit Cost [75]
Anaemia	0.00030	0.00340	3,176 DKK
Fatigue	0.00040	0.00290	4,460 DKK
Febrile Neutropenia	0.00001	0.00880	38,408 DKK
Leukopenia	0.00001	0.00330	25,419 DKK
Neutropenia	0.0002	0.01220	3,176 DKK

Abbreviations: AE – adverse event; DKK - Danish Krones.

8.5.4 Patient and transportation cost (All health states)

Patient and transportation costs are included in the model in line with the DMC method guidelines [34]. The unit cost per patient hour is estimated to be 181 DKK and the transportation cost is estimated to be 3.51 DKK per km with the assumption of an average distance to the hospital of 40 km (roundtrip) in line with the DMC guidelines 2022, see

Table 35 [34,67]. It is further assumed that patients would spend 30 minutes on transportation per visit (roundtrip).

Table 35: Patient and transportation cost per unit

		Reference
Patient cost per hour	181.00 DKK	DMC method guidelines [34,67]
Transportation cost per visit	140.00 DKK	DMC method guidelines [34,67]

Abbreviations: DKK - Danish Krones; DMC – Danish Medicines Council.

Table 36 shows the patient costs associated with the administration of atezolizumab for patients in the DFS health state. Atezolizumab is administered IV, and the consulted Danish clinical experts estimated the administration time for atezolizumab to be 1 hour. Furthermore, Danish clinical experts stated that the patient time associated with consultations are more frequent in the early phase of treatment initiation. The first visits will include a one-hour consultation with a doctor and one hour of administration time with atezolizumab. The clinical experts estimate the following consultations to be 20 minutes and will happen 2 weeks after initiating treatment, one month after the second consultation, two month after the third consultation, followed by every third month. This results in a total of 6 consultations within the treatment period of 11 months [53].

Furthermore, it is stated by the two Danish clinical experts that patients also spend time outside the oncology department for blood samples, ECG, bronchoscopy, and CT scans. The Danish clinical experts stated that blood samples and ECGs are conducted one day before first administration and blood samples again 14 days post-treatment initiation. Blood samples will then be taken one day before each treatment administration [53]. Danish clinical experts estimated blood samples and ECG to take 30 minutes each. Furthermore, the clinical expert estimated the patient time of CT scans to be 1 hour. The clinical experts stated that a baseline CT scan is conducted before first administration, and subsequently monitored every third month [53]. The time usage of the initial bronchoscopy is estimated to be 20 minutes, based on the webpage netdoktor.dk [82]. The estimated patient cost in the DFS health state associated with treatment of atezolizumab in the first model cycle is estimated to be 1,212.70 DKK and following cycles to 829.21 DKK, see Table 36.

Table 36: Patient costs associated with administration of atezolizumab

Patient time	Usage (hours)	Resource use (first cycle) [53,82]	Costs (first cycle)
First model cycle			
Administration	1	1	181.00 DKK
Outpatient consultation	1	1	181.00 DKK
Blood samples	0.5	2	181.00 DKK
Electrocardiogram	0.5	1	90.50 DKK

Bronchoscopy	0.2	1	36.20 DKK
CT-scan	1	1	181.00 DKK
Transportation roundtrip	0.5	4	362.00 DKK
Total cost for the cycle			**1,212.70 DKK**
Patient time	Usage (hours)	Usage per cycles (hours) [53,81]	Costs per cycle
Following model cycles			
Administration	0.5	1	181.00 DKK
Outpatient consultation	0.33	0.63	37.63 DKK
Blood samples	0.5	2	181.00 DKK
CT-scan	1	0.38	68.78 DKK
Transportation roundtrip	0.5	4	362.00 DKK
Total cost per cycle			829.21 DKK

Abbreviations: CT - computed tomography; DKK - Danish Krones.

Table 37 shows the patients time and costs for patients treated with pembrolizumab, cisplatin, vinorelbine, or docetaxel in the health states of locoregional recurrence and 1L/2L metastatic recurrence. Patient time used for the different treatment regimens are based on Danish clinical experts' testimonies.

Patients treated with pembrolizumab in the health state 1L metastatic recurrence were estimated by the two Danish experts to spend three hours including one hour of administration and one hour consultation prior to treatment with a doctor and post treatment monitoring with a nurse. Subsequent treatments with pembrolizumab are estimated to take 1 hour and 45 minutes, including 1 hour of administration time, 30 minutes consultation time with a doctor prior to administration, and 15 minutes consultation time with a nurse post-administration, see Table 37 [53].

Monitoring of patients treated with pembrolizumab, cisplatin, vinorelbine, and docetaxel are according to the consulted Danish clinical experts is the same as for atezolizumab and consequently applicable for both the atezolizumab- and the BSC arm in the model, see Table 36. The patient time for cisplatin is estimated by the consulted Danish clinical experts to be 4 hours including infusion and hydration pre- and post-treatment. Time usage for vinorelbine is estimated to be 10 minutes and 1 hour for docetaxel based on the summary of product characteristics published by EMA [78,83]. Cisplatin and vinorelbine are given as a combination therapy. In order to avoid double counting, time spent on transportation is not considered in the total cost of vinorelbine in Table 37.

Patients off treatment are assumed to receive the same monitoring with consultations and CT-scans every third month, and blood samples once a month resulting in a patient time cost of 421.73 DKK per model cycle.

Table 37: Patient costs associated with treatment with pembrolizumab, cisplatin, vinorelbine, or docetaxel

Patient time	Usage (hours)	Resource use (per cycle) [53,81]	Cost (per cycle)
1st administration pembrolizumab	1	1	181.00 DKK
Administration pembrolizumab	0.5	1	90.50 DKK
Administration cisplatin	4	1	724.00 DKK
Administration vinorelbine	0.17	1	30.77 DKK
Administration docetaxel	1	1	181 DKK
Outpatient consultation	0.75	1	135.75 DKK
1st administration pembrolizumab	1	1	181.00
Administration pembrolizumab	0.5	1	90.50
Total cost first cycle, pembrolizumab			**1,393.70 DKK**
Total cost per cycle, pembrolizumab			**557.48 DKK**
Total cost per cycle, cisplatin			**1,190.98 DKK**
Total cost per cycle, vinorelbine			**30.77 DKK***
Total cost per cycle, docetaxel			**647.98 DKK**
Total cost per cycle, Off treatment			**421.73 DKK**

*Time on consultation, blood samples, CT scans, and transportation is not included as vinorelbine is given in combination with cisplatin. Abbreviation: Danish krones.

The transportation cost for the first treatment cycle of atezolizumab and pembrolizumab is based on the two Danish clinical expert statements. Patients are going to the hospital for a CT scan, bronchoscopy, and blood sample two weeks prior to first administration of treatment, and a blood sample the day before administration, on the day of administration, and at a consultation 2 weeks after the first administration. This results in a transportation cost of 560 DKK in the first cycle for atezolizumab, see

Table 38.

Transportation costs for the following cycles are expected to be similar for all treatments at 405.83 DKK per cycle. For patients off treatment the transportation cost is estimated to be 186.20 DKK per cycle. The difference between the estimation of patients on and off treatment is a result of fewer hospital visits due to no treatment administrations and fewer blood samples, see

Table 38.

Table 38: Transportation cost per cycle

		Reference
Transportation cost first cycle	560.00 DKK	DMC method guidelines [67]
Transportation cost following cycles	405.83 DKK	DMC method guidelines [67]
Transportation cost per cycle, Off treatment	186.20 DKK	DMC method guidelines [67]

8.6 Results

8.6.1 Base case overview

Table 39: Base case overview

Parameter	Value	Rationale
General model parameters		
Time horizon	39 years	Life-time horizon
Discount rate - efficacy	3.5% until year 35 then 2.5%	DMC methods guideline [34]
Discount rate - costs	3.5% until year 35 then 2.5%	DMC methods guideline [34]
Data source	IMpower010, subgroup: PD-L1 ≥50%, Stage II-IIIA, excl. EGFR and ALK+	IMpower010, in line with relevant population in Denmark
Intervention	Atezolizumab	IMpower010
Comparator	BSC	IMpower010
Population parameters		
Age	61 years	IMpower010
Body weight	74 kg	IMpower010
Height	169 cm	IMpower010
Body surface area	1.85 m^2	IMpower010
Efficacy and treatment duration		
Mean TTOT – atezolizumab	8.64 months, as observed in trial	IMpower010

DFS – Atezolizumab arm	Log-logistic	See section 8.3.1.1
DFS – BSC arm	Log-logistic	See section 8.3.1.1
OS – Atezolizumab and BSC arm	Exponential using trial data from: Nakamichi et al. 2017, Kruser et. Al. 2014, IMpower110 trial, Wong et. Al., & OAK trial 2016	See section 8.3.1.1
DFS curve adjustments		See section 8.3.1.2
Treatment effect starts decreasing at	12 months	See section 8.3 – assumption
Treatment effect null at	60 months	See section 8.3 - assumption
Cure proportion starts to increase at	24 months	See section 8.3.2.2
Maximum cure proportion reached at	60 months	See section 8.3 - assumption
Utilities		
DFS – On treatment (Atezolizumab)	0.76	Jang et al. (2010)
DFS – Off treatment (Atezolizumab)	0.76	Jang et al. (2010)
DFS – On treatment (BSC)	0.76	Jang et al. (2010)
DFS – Off treatment (BSC)	0.76	Jang et al. (2010)
Locoregional recurrence (Curative treatment)	0.73	Chouaid et al. (2013)
Locoregional recurrence (Palliative treatment)	0.62	van den Hout et al. 2006
1L metastatic health state (Treatment)	0.71	IMpower150
1L metastatic health state (No treatment)	0.62	van den Hout et al. 2006
2L metastatic health state (Treatment)	0.69	IMpower110
Cost variables		
Drug cost	Adjuvant treatment applied to reflect the real administration, following lines (locoregional, 1L/2L metastatic recurrence) is applied as a monthly cost for both treatment arms.	Reflects the drug costs accrued over the patient's course of treatment
Administration cost	Adjuvant treatment applied to reflect the real administration, following lines (locoregional, 1L/2L metastatic recurrence) is applied as a monthly cost for both treatment arms.	Reflects the administration costs accrued over the patient's course of treatment
AE management cost	One-time cost in the first model cycle for adjuvant treatment (DFS health state), monthly cost for the remaining health state in both treatment arms.	Reflects the AE management costs accrued during treatment

Follow up cost	Applied as monthly costs for both treatment arms. Monthly follow-up costs are not assumed to differ between treatment arms.	Reflects the follow-up costs accrued over the patient's lifetime
Patient and transportation cost	Applied as a monthly cost for both treatment arms.	DMC methods guideline [34]

Abbreviations: 1L – first-line; 2L – second-line; ALK - anaplastic lymphoma kinase; BSC – best supportive care; cm – centimeter; DFS – disease-free survival; DMC – Danish Medicines Council; EGFR - epidermal growth factor receptor; kg – kilograms; m^2 - square meter; OS – overall survival; PD-L1 - programmed death-ligand 1; TTOT - time to off treatment.

8.6.2 Base case results

Base-case results of the economic model with the parameters as discussed and presented in the sections above are presented below, versus Danish standard of care treatment (BSC).

Table 40 provides a summary of the base case results using known list-prices for the various medicines. The analysis is based on pricing based on official PPP from medicinpriser.dk, no discounts included. The intervention is costlier than the comparator for patients in the DFS- and locoregional health states but saves costs in comparison for patients in the following health states "Metastatic recurrence (1L)" and "Metastatic recurrence (2L)". This can be explained by the significantly higher proportion of patients remaining in the DFS health state in the intervention arm versus the comparator, underlining the new intervention's effectiveness. The deterministic ICER is [redacted] per QALY gained, with incremental LYs gained of [redacted]

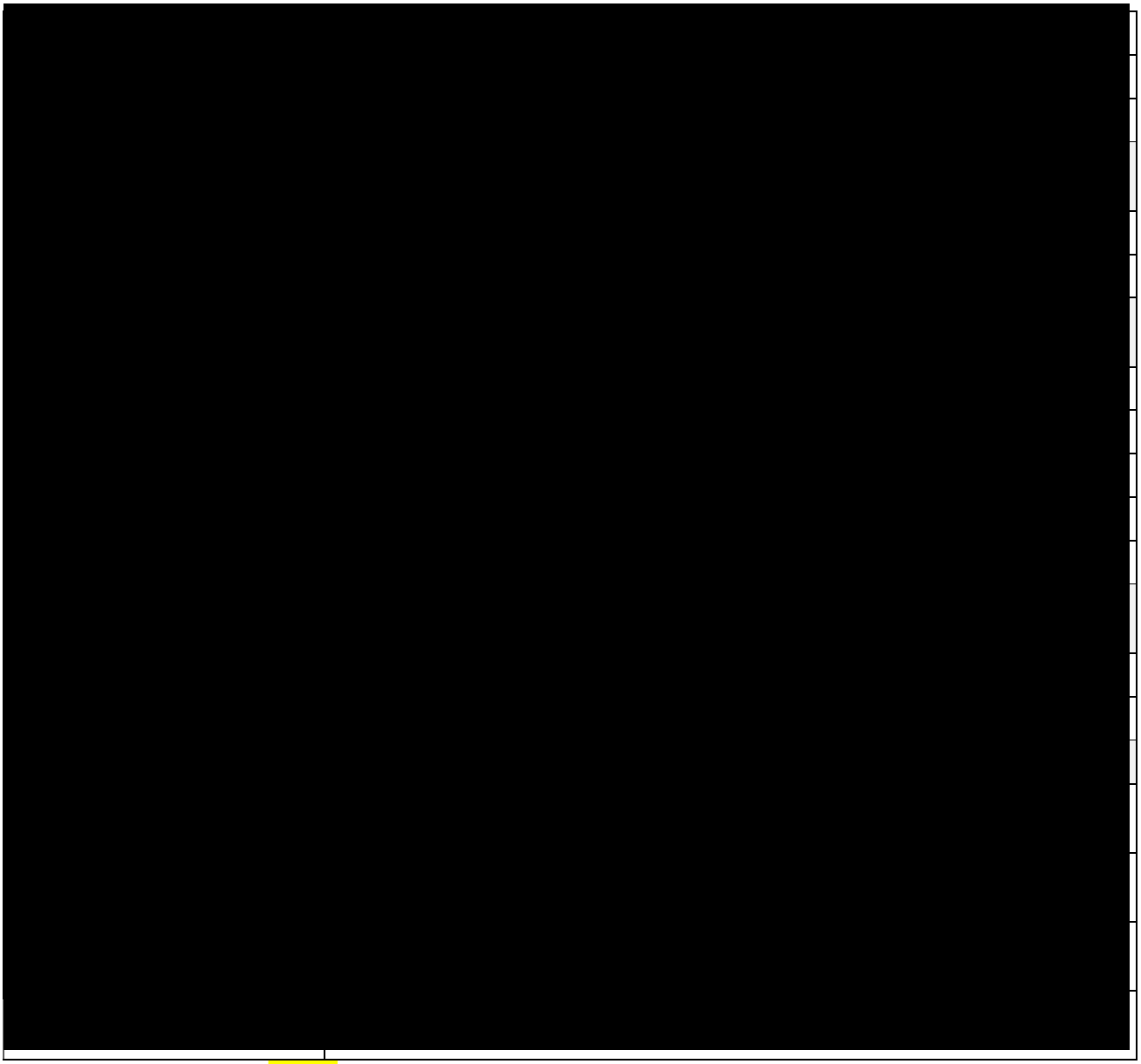
Table 40: Base case results

Per patient	Intervention	Comparator	Difference
Life years gained			
[redacted]			
QALYs			
[redacted]			

[redacted]

Costs

[redacted]



*Assuming a WTP threshold of [redacted]. Abbreviations: 1L – first-line; 2L – second-line; AE – adverse event; BSC – best supportive care; DKK - Danish Krones; ICER - incremental cost-effectiveness ratio; NMB - net monetary benefit; PSA – probabilistic sensitivity analysis; QALY - quality-adjusted life years.

8.7 Sensitivity analyses

To identify key model drivers and the influence of parameter uncertainty, one-way deterministic sensitivity analyses (DSA) are conducted using alternate values for model parameters.

To test the impact of applying different assumptions, scenario analyses are conducted for the key model parameters.

To test the robustness of results with respect to uncertainty in the model input parameters, a PSA is performed using a second-order Monte Carlo simulation. In this analysis, each parameter subject to parameter uncertainty is assigned a probability distribution, and cost-effectiveness results associated with the simultaneous selection of random values from the distribution of each of these parameters were generated. The process was repeated for 1,000 iterations and

results of the PSA were plotted on the cost-effectiveness plane (or scatter plot) and were used to calculate cost-effectiveness acceptability curves (CEACs), highlighting the probability of cost-effectiveness over various willingness to pay thresholds.

8.7.1 Deterministic sensitivity analyses

Impact on the ICER of the range of some key parameters is presented in Figure 20 below. The tornado diagram presents the relative impact some key influential model parameters have on the list-price ICER (per QALY).

Abbreviations: 1L – first-line; 1LMTx - ; 2L – second-line; 2LMTx - ; ATZ – atezolizumab; BSC – best supportive care; DFS – disease-free survival; LR CT - ; PFS – progression-free survival; QALY - quality-adjusted life years.

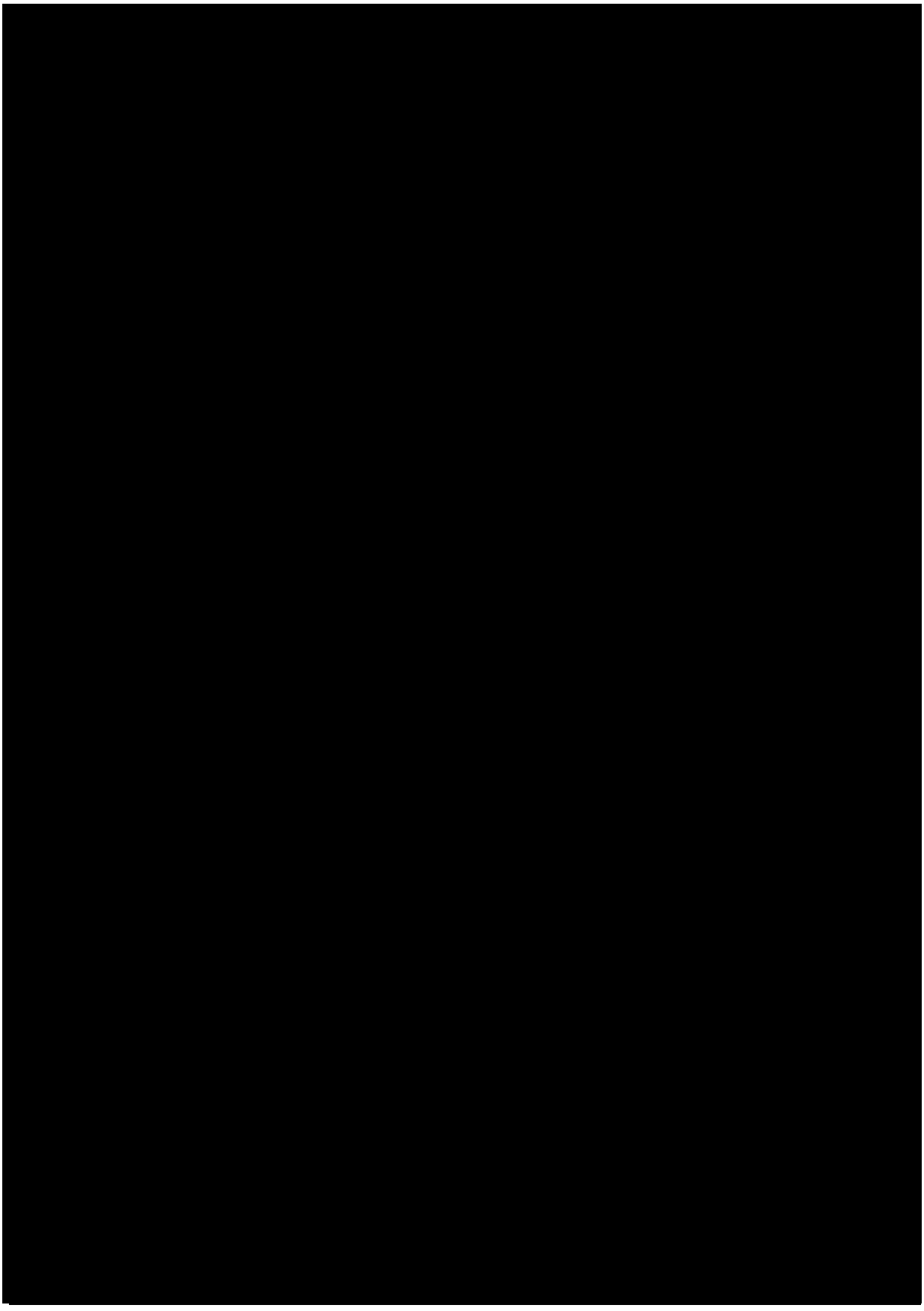
8.7.2 Scenario analyses

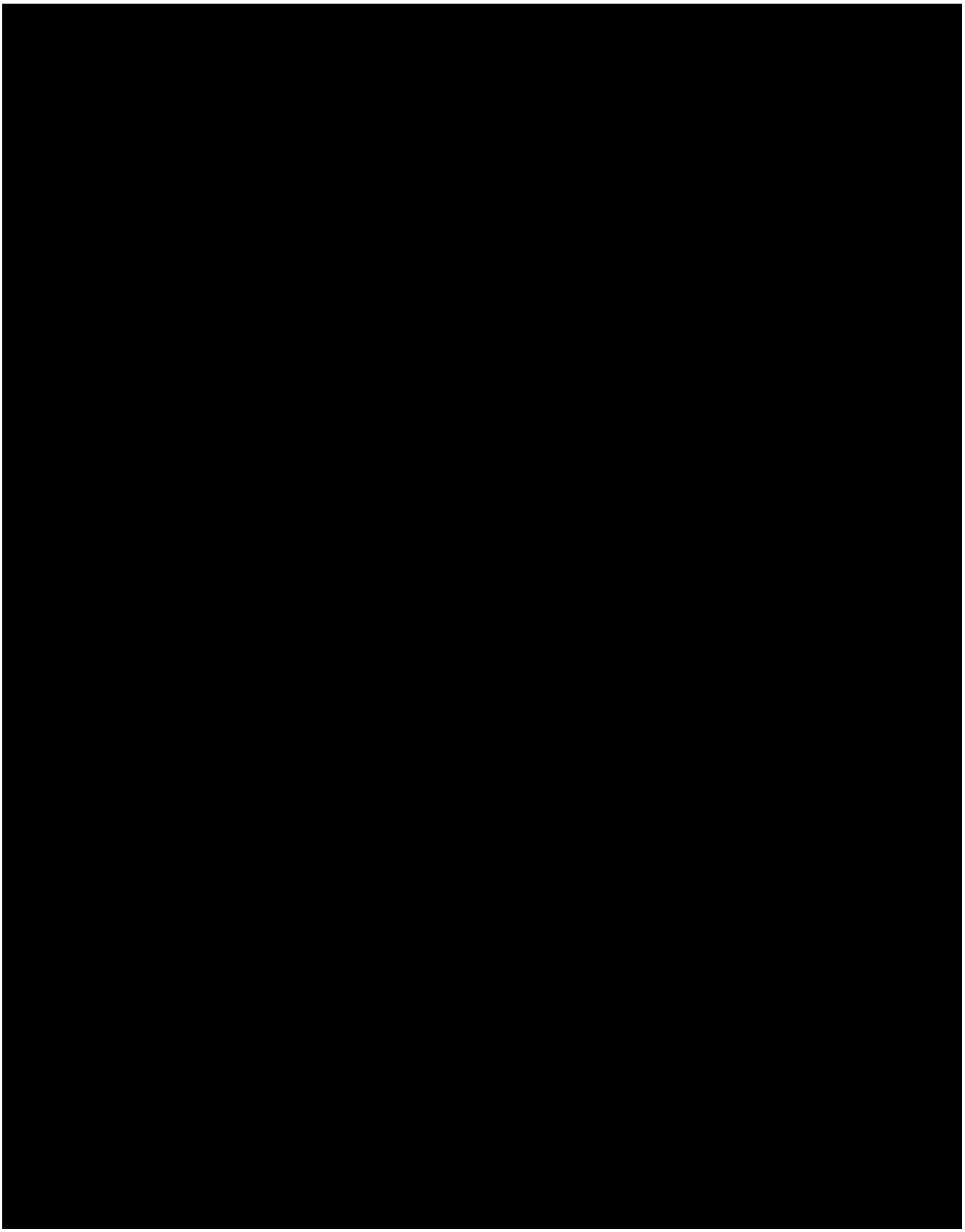
Scenario analyses are performed to explore how changing some of the key model parameters will impact the model results. Table 41 below summarises the main scenario results. The ICER is most noticeably impacted by a drastic reduction of the time horizon, the shortening of treatment effect duration, significant changes to the proportion of patients receiving treatment in 1L metastatic recurrence and using pooled trial data to determine recurrence type. Furthermore, using Exponential, Weibull, or Gamma distributions for DFS in the BSC arm, and cure time points and cure proportions resulted in considerable ICER changes.

Based on the various parameter settings explored in the scenario analyses, the resulting ICERs are all within the range considered cost-effectiveness (i.e., max ICER ranging between . The relatively limited ICER-impact from the majority of the changes to the model parameters indicates that the model result is robust and that the assumptions are well balanced.

Table 41: Scenario analyses exploring changes to key model parameters

Parameter	Inc. cost per QALY ATZ vs BSC average	DKK Δ ICER vs base case





8.7.3 Probabilistic sensitivity analyses

The cost-effectiveness plane and incremental cost-effectiveness plane, illustrating the QALYs and costs and the incremental QALYs and costs, respectively, are presented in Figure 21 and Figure 22 below using list prices. This represents the joint distribution of costs and effect for the intervention (atezolizumab), and the comparator included in the model (BSC) and the incremental results between these. Convergence testing confirmed that 1,000 iterations were sufficient to estimate the probabilistic ICERs (see Appendix K ICER Convergence). The majority of simulated ICERs are located in the NE quadrant, indicating the intervention to be costlier but also more effective than the comparator. The cost-effectiveness plane illustrates very little overlap in both costs and QALYs between the two interventions

To easier communicate the decision uncertainty represented in the cost-effectiveness scatterplot above, the corresponding cost-effectiveness acceptability curve (CEAC) has been illustrated in Figure 23. Each CEAC represents the likelihood of a particular treatment strategy to be cost-effective according to the WTP thresholds. Using the list-price results, at lower WTP values (, BSC has a higher probability of being cost-effective than atezolizumab. For higher WTP values (, atezolizumab has a higher probability to be cost-effective, increasing with WTP threshold progression. Past a WTP of around above, the probability of atezolizumab being cost-effective is over 95%, leaving almost no decision uncertainty.

Abbreviations: ATZ – atezolizumab; BSC – best supportive care; WTP - willingness to Pay.

9. Budget impact analysis

The budget impact model is developed to estimate the expected budget impact of recommending atezolizumab as a treatment option in Denmark. The budget impact analysis has been embedded within the cost-effectiveness model and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the populations in the cost per patient model.

The costs included in the budget impact model are undiscounted, and patient cost and transportation cost have not been included as per the guidelines by the DMC.

The analysis is developed by comparing the costs for the Danish regions per year over five years in the scenario where atezolizumab is recommended as a standard treatment and the scenario where atezolizumab is not recommended as a standard treatment. The total budget impact per year is the difference between the two scenarios.

9.1 Market shares and number of patients

As described in section 5.1, approximately 61 patients are expected to be eligible for adjuvant treatment with atezolizumab in the first year. For the budget impact analysis, 61 patients have been assumed in year 1, 65 new patients in year 2, 70 in year 3, 75 in year 4, and 80 in year 5.

Future market shares depend on multiple factors such as developments in the treatment landscape, and available physical and economic resources. Regardless, the estimates will be associated with uncertainty. However, no adjuvant treatment is available for patients with stage II-IIIA, early NSCLC with PD-L1 expression ≥50%, who is EGFR/ALK+ negative. Therefore, it is assumed that all patients will be treated with atezolizumab if recommended. The potential market share for atezolizumab with or without a recommendation is reported in

Table 42.

Table 42: Number of patients expected to be treated over the next five-year period

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of new eligible patients	67	70	75	80	85
Scenario where atezolizumab is not recommended					
Atezolizumab	0%	0%	0%	0%	0%
BSC	100%	100%	100%	100%	100%
Scenario where atezolizumab is recommended					
Atezolizumab	100%	100%	100%	100%	100%

	Year 1	Year 2	Year 3	Year 4	Year 5
BSC	0%	0%	0%	0%	0%

Abbreviation: BSC - best supportive care.

9.2 Budget impact result

Based on the base case assumptions, the estimated budget impact of recommending atezolizumab as a possible standard treatment in Denmark for patients with NSCLC whose tumours have PD-L1 expression on ≥50% and who are EGFR/ALK+ negative is [redacted]

Table 43: Expected budget impact of recommending atezolizumab as standard treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Without recommendation	[redacted]				
With recommendation					
Budget impact of recommendation					

Abbreviation: DKK – Danish

10. Discussion on the submitted documentation

Clinical assessment

IMpower010 is a randomised, multicentre, open-label, phase III study that provides a direct comparison of atezolizumab with BSC after cisplatin-based chemotherapy. BSC is the preferred choice of comparator based on Danish clinical practice. The population in the study is representative of the Danish target population, and the outcome measures in the study, including DFS, OS and safety, are considered relevant for the target population. The open-label study design gives rise to some limitations. However, because of this, a retrospective blinded independent central review of the primary efficacy endpoint, DFS, was performed in addition to the assessment of DFS by investigators.

IMpower010 is the first phase III study of CIT to demonstrate a DFS improvement in the adjuvant NSCLC setting after cisplatin-based chemotherapy. The study met its primary endpoint at the DFS protocol-specified interim analysis (CCOD: January 21, 2021), demonstrating a statistically significant improvement in DFS with atezolizumab over BSC for PD-L1 TC ≥1% stage II-IIIA NSCLC. A pronounced, clinically meaningful efficacy was seen in a subgroup of patients with PD-L1 TC ≥50% stage II–IIIA NSCLC tumours without EGFR/ALK+. The treatment effect in these patients seemed to be

largely driving the overall treatment effect observed. Therefore, the data for this subpopulation was the basis for the assessment and approval in the EMA and will form the basis for the assessment in the Medicines Council.

Similar to most other studies in early NSCLC [30], DFS was defined as the primary efficacy endpoint of the IMpower010 study. DFS as a surrogate for OS is an accepted endpoint for drug approval by both the EMA and the FDA, as demonstrated with the approval of immune checkpoint inhibitors for adjuvant treatment of several solid tumours [29].

DFS was an exploratory endpoint in the PD-L1 TC ≥50% stage II–IIIA population without EGFR/ALK+. Therefore, analysis in this subgroup was not included in the alpha control of the statistical testing [19]. However, the result of the analysis showed a large effect size of treatment with atezolizumab on DFS. Similar results were observed with the unstratified (included in the statistical analysis plan) and stratified analysis (requested by EMA); the differences between the two HRs were small, the CIs overlapped and did not include 1. The DFS treatment benefit observed in this subpopulation appeared consistent with that observed in the overall PD-L1 TC ≥50% stage II–IIIA population as the HRs remained similar whether patients with EGFR/ALK+ were included or excluded. The DFS benefit was further supported by results from the exploratory analyses of OS, although immature. At the time of the DFS interim analysis, an early OS analysis was conducted (event rates of 9% and 23% in the atezolizumab and BSC arms, respectively). This was before meeting the event numbers necessary for the first pre-specified OS interim analysis [19]. The OS interim analysis was conducted at a median follow-up of 47.7 months (CCOD: April 18, 2022). At this time, the event rate was 14.2% in the atezolizumab and 29.1% in the BSC arm. Results from this analysis confirms the results from the early OS analysis, and indicate, despite being immature, that the benefit in DFS seen with the introduction of atezolizumab in the adjuvant setting is translating into a clinically relevant benefit in OS as it is the case with chemotherapy [84]. Additional OS interim analyses are planned and Roche will provide these data as well as data from the final DFS and OS analyses to EMA once conducted. These data can also be provided to the Medicines Council.

The safety profile of atezolizumab in the adjuvant setting was generally consistent with the previously reported safety profile of atezolizumab monotherapy in the advanced setting. No new safety signals were observed. However, a higher incidence of imAEs were reported in IMpower010 compared with that reported in the pooled atezolizumab monotherapy population. As discussed previously, patients treated in the adjuvant setting may be more susceptible to developing imAEs [27]. A higher rate of discontinuations due to AEs were also observed in IMpower010 compared with the pooled atezolizumab monotherapy safety data. However, it should be noted that about half of the AEs leading to discontinuation in IMpower010 were of grade 1-2, which might indicate that investigators had a lower threshold for discontinuing treatment in patients with early-stage NSCLC due to treatment-related toxicity than might be seen in the metastatic setting [19]. Moreover, the median treatment duration was longer for patients in the adjuvant setting than patients in the metastatic setting. The median number of atezolizumab doses administered was 16 in IMpower010 (maximum allowed per protocol) and 6 in the pooled atezolizumab monotherapy populations [27].

Health economic assessment

For the cost-effectiveness analysis, the clinical efficacy and safety are assessed with direct evidence from IMpower010. Clinical efficacy (in non-metastatic health states) as well as DFS endpoints were directly taken from IMpower010, while OS data is obtained from relevant long term studies and utility values for each health state were sourced from the literature. Results are compared to the current SOC in Denmark, BSC, aligned with Danish guidelines and the comparator arm in the IMpower010 study.

A cost-utility analysis was performed, resulting in a base case ICER of [redacted] The intervention (atezolizumab) is therefore a cost-effective use of Danish health care resources, for

patients with stage II-IIIA, early NSCLC and PD-L1 ≥50%. Probability analyses were also performed to inform about decision uncertainty at various WTP threshold levels. Assuming a WTP of [redacted] treatment with atezolizumab is cost-effective in the majority of the simulations, showcased by ICERs located in the NE quadrant of the CE-plane.

The main uncertainty in this CE model is that only the DFS disease state is informed by the IMpower010 study and consequently relies heavily on external data. This uncertainty cannot be mitigated, however the uncertainty in the structural and parametric assumptions were carried out to demonstrate the overall uncertainty. Finally, considering the significant benefit of atezolizumab versus BSC on DFS, these predicted results are considered plausible.

11. List of experts

[redacted]

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Appendix A Literature search for efficacy and safety of intervention and comparator

The clinical phase III study IMpower010 directly compares atezolizumab with the comparator relevant in Danish clinical practice. The study provides sufficient documentation for efficacy and safety for both the intervention and comparator, and therefore, a literature search for additional evidence has not been performed.

Unpublished data

All data presented from the first CCOD are published. OS data from the second CCOD have been presented at the WCLC on August 6-9, 2022. The presentation has been provided to the Medicines Council as part of the application.

Appendix B Main characteristics of included studies

Trial name: IMpower010	**NCT number: 02486718**
Objective	To investigate the efficacy and safety of atezolizumab vs. best supportive care (BSC) as adjuvant treatment for patients with stage IB-IIIA non-small cell lung cancer (NSCLC) following resection and adjuvant chemotherapy.
Publications – title, author, journal, year	Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Felip et al. The Lancet. 2021 [19]
Study type and design	IMpower010 is a randomised, multicentre, open-label, phase 3 study
Sample size (n)	n=1005

Main inclusion and exclusion criteria	**Inclusion criteria [19,27,85]:** *Inclusion criteria for enrollment phase* ● Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 ● Histological or cytological diagnosis of stage IB (tumours greater than or equal to ≥4 centimetres [cm])-IIIA (T2-3 N0, T1-3 N1, T1-3 N2, T4 N0-1) NSCLC (per the Union Internationale Contre le Cancer staging system (UICC)/American Joint Committee on Cancer staging system (AJCC) staging system, 7th edition; Detterbeck et al. 2009) ● Participants must have had complete resection of NSCLC 4-12 weeks ≥28 days and less than or equal to ≤ 84 days) prior to enrollment and must be adequately recovered from surgery ● If mediastinoscopy was not performed preoperatively, it is required that, at a minimum, mediastinal lymph node systematic sampling will have occurred. Systematic sampling is defined as removal of at least one representative lymph node at specified levels. Mediastinal lymph node dissection (MLND) entails resection of all lymph nodes at those same levels. For a right thoracotomy, sampling or MLND is required at levels 4 and 7 and for a left thoracotomy, levels 5 and/or 6 and 7. Exceptions will be granted if there is clear documentation in the operative report or in a separately submitted addendum by the surgeon of exploration of the required lymph node areas, the participant will be considered eligible if no lymph nodes are found in those areas; if participants have documented N2 disease in one level (per the UICC/AJCC staging system, 7th edition; Detterbeck et al. 2009), not all levels need to be sampled; if the preoperative staging imaging results (contrast computed tomography [CT] and positron emission tomography [PET] scans) do not suggest evidence of disease in the mediastinum, the participant will be considered eligible if N2 nodal sampling is not performed per surgeon's decision ● Eligible to receive a cisplatin-based chemotherapy regimen ● Adequate hematologic and end-organ function as defined in protocol ● For women of childbearing potential and men with partners of childbearing potential, agreement to use a highly effective form(s) of contraception during study treatment that resulted in a low failure rate of <1% per year when used consistently and correctly *Inclusion criteria for randomised phase* ● Women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of atezolizumab or BSC ● Adequate hematologic and end-organ function as defined in protocol **Exclusion criteria [19,27,85]:** *Exclusion criteria for enrollment phase* ● Illness or condition that may interfere with a participant's capacity to understand, follow, and/or comply with study procedures ● Pregnant and lactating women ● Treatment with prior systemic chemotherapy: Chemotherapy for early stage of malignancy with curative intent, provided that the last dose received was more than 5 years prior to enrollment and low-dose chemotherapy for non-malignant conditions is allowed ● Hormonal cancer therapy or radiation therapy as prior cancer treatment within 5 years before enrolment ● Treatment with any other investigational agent with therapeutic intent within 28 days prior to enrolment

	• A hearing loss (measured by audiometry) of 25 dB at two contiguous frequencies (audiometry will only be required for patients who have suspected or definitive hearing loss) • Known sensitivity to any component of the chemotherapy regimen the participant will be assigned to, or to mannitol • Prior treatment with cluster of differentiation (CD) 137 (CD137) agonists or immune checkpoint blockade therapies, anti-programmed death-1 (PD-1), and anti programmed death ligand 1 (PD-L1) therapeutic antibodies • Malignancies other than NSCLC within 5 years prior to randomisation, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS greater than [>] 90 percent [%]) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localised prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent) • History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanised antibodies or fusion proteins • Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation • History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis • Positive test for human immunodeficiency virus • Participants with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen test at screening) or hepatitis C • Active tuberculosis • Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within the previous 3 months, unstable arrhythmias, or unstable angina • History of idiopathic pulmonary fibrosis, organising pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan • Prior allogeneic bone marrow transplantation or solid organ transplant • Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the participant at high risk from treatment complications • Known tumour PD-L1 expression status as determined by an immunohistochemistry assay from other clinical studies (e.g., participants whose PD-L1 expression status was determined during screening for entry into a study with anti-PD-1 or anti-PD-L1 antibodies but were not eligible are excluded) *Specific exclusions for pemetrexed treatment* • Participants with squamous cell histology *Exclusion criteria for randomised phase* • Signs or symptoms of infection within 14 days prior to randomisation (severe infection within 28 days prior to randomisation), including but not limited to hospitalisation for complications of infection, bacteremia, or severe pneumonia • Received therapeutic oral or intravenous (IV) antibiotics within 14 days prior to randomisation • Major surgical procedure within 28 days prior to randomisation or anticipation of need for a major surgical procedure during the course of the study

Trial name: IMpower010	NCT number: 02486718
	• Administration of a live, attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation that such a live attenuated vaccine will be required during the study • Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to randomisation: Prior treatment with cancer vaccines is allowed • Treatment with systemic corticosteroids or other immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumour necrosis factor agents) within 14 days prior to randomisation
Intervention	Atezolizumab (1200 mg IV) every 3 weeks for 16 cycles (cycle length=21 days), n=507
Comparator(s)	Best supportive care, n=498
Follow-up time	The median duration of follow-up for the primary endpoint (DFS) was 32.8 months. The median duration of follow-up for the DFS analysis in the PD-L1 ≥50% stage II-IIIA population was 34.2 months.
Is the study used in the health economic model?	Yes

Trial name: IMpower010	NCT number: 02486718
Primary, secondary and exploratory endpoints	**Primary endpoints:** ● Investigator-assessed disease-free survival (DFS) assessed using Computed Tomography (CT)/Magnetic Resonance Imaging (MRI)/X-Ray [Time Frame: From randomization to the date of first recurrence of NSCLC, occurrence of new primary NSCLC, or death from any cause, whichever occurs first (up to approximately 131 months)]. DFS will be assessed by the investigator in three primary analysis populations: Patients with NSCLC stage II–IIIA and tumours with PD-L1 TC ≥1% (per SP263 IHC assay), all randomised patients with NSCLC stage II-IIIA and any PD-L1 expression, and lastly the intention-to-treat (ITT) population (patients with NSCLC stage IB–IIIA and any PD-L1 expression). **Secondary endpoints:** ● Overall survival (OS) in the ITT population [Time Frame: Baseline up to death from any cause (up to approximately 131 months)]. ● Percentage of participants who are disease-free at Year 3, assessed using CT/MRI/X-Ray [Time Frame: Year 3]. DFS rates will be measured in the PD-L1 TC ≥1% subpopulation within the stage II-IIIA population, in all randomised patients with stage II-IIIA NSCLC, and in the ITT population. ● Percentage of participants who are disease-free at Year 5, assessed using CT/MRI/X-Ray [Time Frame: Year 5]. DFS rates will be measured in the PD-L1 TC ≥1% subpopulation within the stage II-IIIA population, in all randomised patients with stage II-IIIA NSCLC, and in the ITT population. ● DFS in the PD-L1 TC ≥50% subpopulation (defined as ≥50% TC expression by the SP263 IHC assay) in patients with stage II-IIIA NSCLC [Time Frame: From randomization to the date of first recurrence of NSCLC, occurrence of new primary NSCLC, or death from any cause, whichever occurs first (up to approximately 67 months)].
Method of analysis	The Kaplain-Meier method was used to calculate median DFS and DFS rates. The Brookmeyer-Crowley method and Greenwood's formula were used to establish the respective 95% confidence intervals (Cis). Hazard rations (HRs) for disease-free survival were estimated by a Cox regression model including two-sided 95% CIs and treatment comparisons were based on the stratified log-rank test. Prespecified subgroup analyses to assess consistency of treatment effect on DFS were done with unstratified HRs estimated from a Cox proportional-hazards model. Safety was analysed in the safety population defined as all patients randomly assigned who received atezolizumab or BSC. Statistical analyses were completed with SAS version 9.4. The statistical analysis plan is available in the supplementary material of Felip et al. 2021 [19].

Trial name: IMpower010	NCT number: 02486718
Subgroup analyses	• Age • Sex • Race and ethnicity • Tumour stage • PD-L1 expression level • Chemotherapy regimen before randomisation • Histology • Smoking history • ECOG performance status
Other relevant information	Not applicable (N/A)

Abbreviations are explained in the text.

Trial name: IMpower110	NCT number: 02409342
Objective	Evaluate the efficacy and safety of atezolizumab compared with chemotherapy consisting of a platinum agent (cisplatin or carboplatin per investigator discretion) combined with either pemetrexed (non-squamous disease) or gemcitabine (squamous disease) in programmed death-ligand 1 (PD-L1)-selected, chemotherapy-naive participants with Stage IV Non-Squamous or Squamous non-small cell lung cancer (NSCLC).
Publications – title, author, journal, year	Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. Herbst RS, et al. N Engl J Med. 2020 Oct 1;383(14):1328-1339 plus Suppl. doi: 10.1056/NEJMoa1917346.
Study type and design	Randomized, open label, phase 3 study. Patients were randomised 1:1 to atezolizumab (1200 mg iv) or 4-6 cycles of platinum-based chemotherapy every 3 weeks. Randomization was stratified according to sex (male vs. female), ECOG performance-status score (0 vs. 1), histologic type (non-squamous vs. squamous), and PD-L1 status (≥1% PD-L1 expression on tumor cells and any level of PD-L1 expression on tumor-infiltrating immune cells vs. <1% PD-L1 expression on tumor cells and ≥1% PD-L1 expression on tumor-infiltrating immune cells). Continuation of atezolizumab after disease progression was allowed in patients who had continued clinical benefit. No crossover to the atezolizumab group was permitted.
Sample size (n)	554
Main inclusion and exclusion criteria	**Inclusion criteria:** • Aged ≥18 years • Histologically or cytologically confirmed, Stage IV non-squamous or squamous NSCLC • No prior treatment for Stage IV non-squamous or squamous NSCLC. Participant known to have a sensitizing mutation in the epidermal growth factor receptor (EGFR) gene or an anaplastic lymphoma kinase (ALK) fusion oncogene are excluded from the study • Tumor PD-L1 expression as determined by immunohistochemistry (IHC) assay of archival tumor tissue or tissue obtained at screening • Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1

	• Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) • Adequate hematologic and end-organ function Exclusion criteria: • Known sensitizing mutation in the EGFR gene or ALK fusion oncogene • Active or untreated central nervous system (CNS) metastases as determined by Computed Tomography (CT) or magnetic resonance imaging (MRI) evaluation • Malignancies other than NSCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome • Pregnant or lactating women • History of autoimmune disease • History of idiopathic pulmonary fibrosis, organizing pneumonia, drug induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted • Positive test for Human Immunodeficiency Virus (HIV) • Active hepatitis B or hepatitis C • Prior treatment with cluster of differentiation (CD) 137 agonists or immune checkpoint blockade therapies, anti PD1, and anti-PD-L1 therapeutic antibody • Severe infection within 4 weeks prior to randomization • Significant history of cardiovascular disease
Intervention	Atezolizumab 1200 mg is administered as intravenous infusion every 21 days until loss of clinical benefit (as assessed by the investigator), unacceptable toxicity, or death (maximum up to approximately 58 months). N= 277
Comparator(s)	Chemotherapy 4-6 cycles every 3 weeks. Chemotherapy for non-squamous patients: N= 193. Cisplatin 75 mg/m^2 OR Carboplatin: AUC 6 + Pemetrexed 500 mg/ m^2. Pemetrexed maintenance until disease progression Chemotherapy for squamous patients: N=84. Cisplatin 75 mg/ m^2 + Gemcitabine 1200 mg/ m2 OR Carboplatin AUC 5 + Gemcitabine 1000 mg/ m^2. Then best supportive care until disease progression N= 277 (193 non-squamous; 84 squamous)
Follow-up time	At primary analysis the data cutoff date, September 10, 2018, the median follow-up times for survival among patients with EGFR and ALK wild-type tumors who had high PD-L1 expression, high or intermediate PD-L1 expression, and any PD-L1 expression were 15.7 months (range 0 to 35), 15.2 months (range 0 to 35), and 13.4 months (range 0 to 35), respectively. Tecentriq SmPc includes an exploratory OS analysis with longer follow up of median: 31.3 months.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoint**

	• Overall Survival (OS) in the TC3 or IC3-WT Populations and Overall Survival (OS) in the TC2/3 or IC2/3-WT and TC1/2/3 or IC1/2/3-WT Populations. OS is defined as the time from randomization to death from any cause. **Secondary endpoints** • Progression-free survival (PFS) as assessed by the investigator, in TC3 or IC3-WT Populations and the TC2/3 or IC2/3-WT and TC1/2/3 or IC1/2/3-WT Populations according to RECIST version 1.1. • Objective response (ORR) according to RECIST version 1.1 • Duration of response (DOR), landmark OS at 1 year and 2 years • Time to Deterioration (TTD) in Patient-reported Lung Cancer Symptoms Score as Assessed by the Symptoms in Lung Cancer (SILC) Scale Symptom Score • TTD as Assessed Using European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core (EORTC QLQ-C30) • TTD as Assessed Using EORTC QLQ Supplementary Lung Cancer Module (EORTC QLQ-LC13) • Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs). Safety was assessed in all the patients who received a trial agent regardless of PD-L1 expression status or status with respect to EGFR or ALK alterations. OS in Participants with PD-L1 Expression defined with SP263 IHC assay. • Investigator-Assessed PFS in Participants with PD-L1 Expression defined with SP263 IHC assay • OS in Participants with Blood Tumor Mutational Burden (bTMB) • Investigator-Assessed PFS in Participants with bTMB According to RECIST v1.1 • Minimum Observed Serum Concentration (Cmin) of Atezolizumab • Maximum Observed Serum Concentration (Cmax) of Atezolizumab • Percentage of Participants With Anti-therapeutic Antibodies (ATAs) Exploratory endpoints: Overall survival and investigator assessed PFS according to RECIST vs.1.1 in prespecified subgroups with respect to PD-L1 expression defined by the 22C3 IHC assay.
Method of analysis	The primary endpoint overall survival was tested hierarchically in the wild-type population: high PD-L1 expression (TC3 or IC3), then combined high or intermediate PD-L1 expression (TC2/3 or IC2/3) and finally any PD-L1 expression (TC1/2/3 or IC1/2/3). If the results for the primary end points of overall survival were significant for all three populations, a two-sided significance level of 0.05 would be passed to compare progression free survival between study arms. An interim analysis of overall survival was conducted when approximately 96 deaths and an event–patient ratio of 45% had occurred among patients with EGFR and ALK wild-type tumors, who had high PD-L1 expression. Analyses of overall and progression-free survival were performed with the use of a stratified log-rank test. Hazard ratios and 95% confidence intervals were estimated with a stratified Cox regression model. The Kaplan–Meier method was used to estimate medians, and the Brookmeyer–Crowley method was used to generate 95% confidence intervals for the medians. The percentages of patients with a response and

	95% confidence intervals were calculated with the Clopper–Pearson method. Response duration was estimated with the Kaplan–Meier method.
Subgroup analyses	Prespecified subgroup analyses were used to assess the consistency of the treatment effect using unstratified hazard ratios that were estimated from a Cox proportional-hazards model. The subgroups were age, sex, race, ECOG persormance status, histologic type and history of tobacco use. Overall survival and investigator assessed progression-free survival according to RECIST, version 1.1, in prespecified subgroups with respect to PD-L1 expression defined by the SP263 immunohistochemical assay and a exploratory analysis included overall survival and investigator- assessed progression-free survival in prespecified subgroups with respect to PD-L1 expression defined by the 22C3 immunohistochemical assay were performed. Key baseline characteristics for each biomarker subgroup population were consistent with those for the patients in the wildtype, any PD-L1 population. Blood based tumor mutational burden was evaluated in 389 patients. Baseline characteristics for the subgroup were consistent to any PD-L1 expression population.
Other relevant information	Test used for PD-L1 expression testing: VENTANA SP142 IHC assay

Abbreviations are explained in the text. Study is used in the health economic model only. Information source: [41,86]

Trial name: IMpower150	**NCT number: 02366143**
Objective	To investigate the safety and efficacy of in combination with carboplatin+paclitaxel with or without bevacizumab compared with treatment with carboplatin+paclitaxel+bevacizumab in chemotherapy-naïve participants with Stage IV non-squamous non-small cell lung cancer (NSCLC).
Publications – title, author, journal, year	Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. Socinski et al. N Engl J Med 2018;378:2288-301. DOI: 10.1056/NEJMoa1716948 IMpower150 Final Overall Survival Analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in First-Line Metastatic Nonsquamous NSCLC. Socinski et al. J Thorac Oncol. 2021 Nov;16(11):1909-1924. doi: 10.1016/j.jtho.2021.07.009. Epub 2021 Jul 24.
Study type and design	IMpower150 is a randomized, open-label phase 3 study
Sample size (n)	n = 1202

Trial name: IMpower150	NCT number: 02366143
Main inclusion and exclusion criteria	**Inclusion Criteria** • Eastern Cooperative Oncology Group performance status 0 or 1 • Histologically or cytologically confirmed, Stage IV non-squamous NSCLC • Participants with no prior treatment for Stage IV non-squamous NSCLC • Known PD-L1 status as determined by immunohistochemistry assay performed on previously obtained archival tumor tissue or tissue obtained from a biopsy at screening • Measurable disease as defined by RECIST v1.1 • Adequate hematologic and end organ function **Exclusion Criteria** Cancer-Specific Exclusions: • Active or untreated central nervous system metastases • Malignancies other than NSCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome General Medical Exclusions: • Pregnant or lactating women • History of autoimmune disease • History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted • Positive test for human immunodeficiency virus • Active hepatitis B or hepatitis C • Severe infection within 4 weeks prior to randomization • Significant cardiovascular disease • Illness or condition that interferes with the participant's capacity to understand, follow and/or comply with study procedures Exclusion Criteria Related to Medications: • Prior treatment with cluster of differentiation 137 agonists or immune checkpoint blockade therapies, anti-programmed death-1, and anti-PD-L1 therapeutic antibodies
Intervention	Arm A: Atezolizumab+Carboplatin+Paclitaxel (ACP), n = 402 Arm B: Atezolizumab+Carboplatin+Paclitaxel+Bevacizumab (ABCP), n = 400 Atezolizumab was administered as IV infusion at a dose of 1200 milligrams (mg) on Day 1 of each 21-day cycle until loss of clinical benefit. Carboplatin was administered at area under the concentration-time curve (AUC) 6 milligrams per milliliter per minute (mg/mL/min) on Day 1 of each 21-day cycle for 4 or 6 cycles or until loss of clinical benefit whichever occurs first. Paclitaxel was administered as IV infusion at a dose of 200 milligrams per square meter (mg/m^2) on Day 1 of each 21-day cycle for 4 or 6 cycles or until loss of clinical benefit whichever occurs first. Bevacizumab was administered as IV infusion at a dose of 15 milligrams per kilogram (mg/kg) on Day 1 of each 21-day cycle until progressive disease, unacceptable toxicity, or death.

Trial name: IMpower150	NCT number: 02366143
Comparator(s)	Arm C: Carboplatin+Paclitaxel+Bevacizumab (BCP), n = 400 See administration details above.
Follow-up time	CCOD Sep 15, 2017 (progression-free survival (PFS) final analysis): median follow-up of 15.4 months in the ABCP group and 15.5 months in the BCP group CCOD Jan 22, 2018 (overall survival (OS) interim analysis): median follow-up of approximately 29 months CCOD Sep 13, 2019 (OS final analysis): median follow-up of approximately 39.8 months
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints	**Primary endpoints** 1. PFS, as Determined by the Investigator in Arm B Versus Arm C in the effector T-cell (Teff)-high WT Population and intent-to-treat (ITT) wild type (WT) Population [Time Frame: Baseline until disease progression or death, whichever occurs first until data cut-off on 15 September 2017 (up to approximately 29 months)] o PFS, as Determined by the Investigator using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Arm B versus Arm C in the T-effector (Teff)-high WT population and the ITT-WT population. 2. OS in Arm B Versus Arm C in ITT-WT Population [Time Frame: Baseline until death until data cut-off on 22 January 2018 (up to approximately 34 months)] o OS in Arm B Versus Arm C in ITT-WT Population 3. OS in Arm A Versus Arm C in ITT-WT Population [Time Frame: Baseline until death (up approximately 53 months)] o OS in Arm A Versus Arm C in ITT-WT Population **Secondary endpoints:** 1. PFS, as Determined by the Independent Review Facility (IRF) in Arm B Versus Arm C in Teff-High-WT Population and ITT-WT Population [Time Frame: Baseline until disease progression or death, whichever occurs first (up to approximately 29 months)] a. PFS, as determined by the independent review facility (IRF) Using RECIST v1.1 in Arm B versus Arm C in the T-effector (Teff)-high wild type (WT) population and the intent-to-treat (ITT)-WT population. 2. PFS, as Determined by the Investigator in Arm B Versus Arm C in Teff High Population and ITT Population [Time Frame: Baseline until disease progression or death, whichever occurs first (up to approximately 29 months)] a. PFS, as determined by the investigator according to RECIST v1.1, in Arm B versus C in the Teff high population and ITT population. 3. PFS, as Determined by the Investigator in Arm A Versus Arm B in Teff High-WT Population and ITT-WT Population [Time Frame: Baseline until disease progression or death, whichever occurs first (up to approximately 29 months)] a. PFS, as determined by the investigator according to RECIST v1.1, in Arm A versus B in the Teff high-WT population and ITT-WT population. 4. PFS, as Determined by the Investigator in Arm B Versus Arm C by PD-L1 Subgroup [Time Frame: Baseline until disease progression or death, whichever occurs first (up to approximately 29 months)] a. PFS as Determined by the Investigator according to RECIST v1.1, in Arm B Versus Arm C by PD-L1 Subgroup: TC2/3 or 1C2/3 and TC1/2/3 or IC1/2/3 (ITT-WT Population) 5. OS in Arm B Versus Arm C by PD-L1 Subgroup [Time Frame: Baseline until death (up to approximately 34 months)] a. OS in Arm B Versus Arm C by PD-L1 Subgroup: TC2/3 or 1C2/3 and TC1/2/3 or IC1/2/3 (ITT-WT Population) 6. OS in Arm A Versus Arm C by PD-L1 Subgroup [Time Frame: Baseline until death (up approximately 53 months)] a. OS in Arm A Versus Arm C by PD-L1 Subgroup: TC2/3 or 1C2/3 and TC1/2/3 or IC1/2/3 (ITT-WT Population)

	7. OS in Arm B Versus Arm C in Teff High-WT Population, Teff High Population, and ITT Population [Time Frame: Baseline until death (up to approximately 34 months)] 8. OS in Arm A Versus Arm C in Teff High-WT Population, Teff High Population, and ITT Population [Time Frame: Baseline until death (up approximately 53 months)] 9. OS in Arm A Versus Arm B in Teff High-WT Population and ITT-WT Population [Time Frame: Baseline until death (up approximately 53 months)] 10. Duration of Response (DOR), as Determined By Investigator in Arm B Versus Arm C [Time Frame: Baseline until disease progression or death, whichever occurs first (up to approximately 29 months)] a. DOR, as determined by investigator according to RECIST v1.1 in Arm B versus Arm C in the Teff high-WT population and the ITT-WT population. 11. Percentage of Participants With an Objective Response (OR) (Complete Response [CR] or Partial Response [PR]) as Determined by the Investigator in the Teff-High-WT Population and ITT-WT Population [Time Frame: Baseline until disease progression or death, whichever occurs first (up to approximately 29 months)] a. Percentage of Participants With an Objective Response (OR) (Complete Response [CR] or Partial Response [PR]) as Determined by the Investigator using RECIST v1.1 in the Teff-High-WT population and ITT-WT population. 12. OS Rates at Years 1 and 2 in Arm B Versus Arm C [Time Frame: Baseline to 2 years or death, whichever occurs first.] a. OS at 1- and 2-year landmark timepoints in Teff-high WT population and ITT-WT population. 13. OS Rates at Years 1 and 2 in Arm A Versus Arm C [Time Frame: Baseline to 2 years or death, whichever occurs first.] a. OS at 1- and 2-year landmark timepoints in Teff-high WT population and ITT-WT population. 14. Time to Deterioration (TTD) in Patient-Reported Lung Cancer Symptoms Determined by European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire-Core 30 (QLQ-C30) Score [Time Frame: Baseline up to approximately 29 months] a. EORTC QLQ-C30 is a validated & reliable self-report measure (Aaronson et al.1993;Fitzsimmons et al.1999) that consists of 30 questions that assess 5 aspects of patient functioning (physical,emotional,role, cognitive,and social), 3 symptom scales (fatigue,nausea & vomiting, pain),global health/quality of life,and six single items (dyspnea,insomnia, appetite loss,constipation,diarrhea, and financial difficulties). EORTC QLQ-C30 is scored according to the EORTC scoring manual (Fayers et al. 2001). All EORTC scales and single-item measures are linearly transformed so that each score has a range of 0-100. A high score for a functional/global health status scale represents a high or healthy level of functioning/HRQoL (Health-Related Quality of Life);however a high score for a symptom scale or item represents a high level of symptomatology or problems. A ≥10-point change in the symptoms subscale score is perceived by patients as clinically significant (Osoba et al.1998). 15. TTD in Patient-Reported Lung Cancer Symptoms as Determined by EORTC Quality-of-Life Questionnaire-Core Lung Cancer Module 13 (QLQ-LC13) Score [Time Frame: Baseline up to approximately 29 months] a. QLQ-LC13 Quality-of-Life Questionnaire Lung Cancer Module incorporates one multiple-item scale to assess dyspnea and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy,

	alopecia, and hemoptysis. The EORTC QLQ-LC13 is scored according to the EORTC scoring manual (Fayers et al. 2001). All EORTC scales and single-item measures are linearly transformed so that each score has a range of 0-100. A high score for a functional/global health status scale represents a high or healthy level of functioning/HRQoL (Health-Related Quality of Life); however, a high score for a symptom scale or item represents a high level of symptomatology or problems. A ≥10-point change in the symptoms subscale score is perceived by patients as clinically significant (Osoba et al. 1998). 16. Change From Baseline in Patient-Reported Lung Cancer Symptoms Score Using the Symptoms in Lung Cancer (SILC) Scale [Time Frame: Baseline up to approximately 29 months] a. The SILC (Symptoms in Lung Cancer) scale was used to assess patient-reported severity of lung cancer symptoms (chest pain, dyspnea, and cough). The SILC scale is a 9-item content validated self-report measure of lung cancer symptoms. It measures severity of cough, dyspnea, and chest pain with a symptom severity score. The SILC questionnaire comprises three individual symptoms (dyspnea, cough, chest pain) and are scored at the individual symptom level, thus have a dyspnea score, chest pain score, and cough score. Each individual symptom score is calculated as the average of responses for the symptom items [e.g. Chest Pain Score=mean (item 1; item 2)]. An increase in score is suggestive of a worsening in symptomology (i.e. frequency or severity). A score change of ≥0.3 points for the dyspnea and cough symptom scores is considered to be clinically significant; whereas a score change of ≥0.5 points for the chest pain score is considered to be clinically significant. 17. Percentage of Participants With Adverse Events [Time Frame: Baseline up to data cutoff date 7 December 2020 (up to approximately 68 months)] a. Percentage of participants with at least one adverse event. 18. Percentage of Participants With Anti-Therapeutic Antibodies (ATAs) to Atezolizumab [Time Frame: Baseline up to approximately 29 months] 19. Maximum Observed Serum Concentration (Cmax) of Atezolizumab in Arm A and Arm B [Time Frame: Day 1 of Cycle 1 and 3 (Cycle length=21 days)] a. The predose samples will be collected on the same day of treatment administration. The infusion duration of atezolizumab will be of 30-60 minutes. 20. Minimum Observed Serum Concentration (Cmin) of Atezolizumab Prior to Infusion in Arm A and Arm B [Time Frame: Day 21 of Cycles 1, 2 3, and 7 (Cycle length=21 days)] 21. Plasma Concentrations for Carboplatin in Arm A, Arm B, and Arm C [Time Frame: Predose (same day of treatment administration), 5-10 minutes before end of carboplatin infusion, 1 h after carboplatin infusion (infusion duration=15 to 30 minutes) on D1 of Cy1,3 (Cycle length=21 days)] 22. Plasma Concentrations for Paclitaxel in Arm A, Arm B, and Arm C [Time Frame: Predose (same day of treatment administration), 5-10 minutes before end of paclitaxel infusion, 1 h after paclitaxel infusion (infusion duration=3 h) on D1 of Cy1,3 (Cycle length=21 days)] 23. Cmax of Bevacizumab in Arm B and Arm C [Time Frame: Cycle 1 Day 1 and Cycle 3 Day 1 (Cycle length=21 days)]

Trial name: IMpower150	NCT number: 02366143
	24. Cmin of Bevacizumab in Arm B and Arm C [Time Frame: Cycle 1 Day 1 and Cycle 2 Day 21 (Cycle length=21 days)]
Method of analysis	The primary analyses of progression-free survival and overall survival in the WT population were performed with the use of a stratified log rank test, in which the stratification factors were those used during randomization (i.e., sex, presence or absence of liver metastases at baseline, and PD-L1 tumor expression). The stratification factors used in the analysis of progression-free survival in the Teff-high WT population were sex and the presence or absence of liver metastases at baseline. Hazard ratios were estimated with the use of a stratified Cox regression model, and the Brookmeyer–Crowley method was used to calculate 95% confidence intervals. The Kaplan–Meier method was used to estimate medians. Full details of the statistical analysis plan are provided in the protocol.
Subgroup analyses	Prespecified subgroup analyses to assess the consistency of the treatment effect, using unstratified hazard ratios that were estimated from a Cox proportional-hazards model.
Subgroup analyses	N/A

Abbreviations are explained in the text. Study is used in the health economic model only. Information source: [38,87]

Trial name: OAK	NCT number: 02008227
Objective	To investigate the efficacy and safety of atezolizumab compared with docetaxel in participants with locally advanced or metastatic NSCLC after failure with platinum-containing chemotherapy.
Publications – title, author, journal, year	Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Rittmeyer et al. The Lancet Volume 389, Issue 10066, P255-265, January 21, 2017. DOI:https://doi.org/10.1016/S0140-6736(16)32517-X
Study type and design	OAK is a multicenter, open-label, randomized, controlled phase 3 study.
Sample size (n)	N = 850 (primary efficacy analysis)

Trial name: OAK	NCT number: 02008227
Main inclusion and exclusion criteria	**Inclusion Criteria** • Locally advanced or metastatic (Stage IIIB, Stage IV, or recurrent) NSCLC • Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens • Disease progression during or following treatment with a prior platinum-containing regimen for locally advanced, unresectable/inoperable or metastatic NSCLC or disease recurrence within 6 months of treatment with a platinum-based adjuvant/neoadjuvant regimen or combined modality (e.g., chemoradiation) regimen with curative intent • Measurable disease, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 **Exclusion Criteria** • Known active or untreated central nervous system (CNS) metastases • Malignancies other than NSCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome • History of autoimmune disease • History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest computed tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted • Active hepatitis B or hepatitis C • Prior treatment with docetaxel • Prior treatment with cluster of differentiation 137 (CD137) agonists, anti-cytotoxic-T-lymphocyte-associated antigen 4 (anti-CTLA4), anti-programmed death-1 (anti-PD-1), or anti-PD-L1 therapeutic antibody or pathway-targeting agents
Intervention	Atezolizumab: 1200 mg IV infusion on Day 1 of each 21-day cycle, n = 425
Comparator(s)	Docetaxel: 75 mg/m^2 IV infusion on Day 1 of each 21-day cycle, n = 425
Follow-up time	CCOD July 7, 2016 (primary analysis): median follow-up was 21 month
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints	**Primary endpoints** 1. Percentage of Participants Who Died: PP-ITT [Time Frame: Baseline until death due to any cause (up to approximately 2.25 years)] 2. Percentage of Participants Who Died: Tumor Cells (TC)1/2/3 or Tumor-Infiltrating Immune Cells (IC)1/2/3 Subgroup of PP [Time Frame: Baseline until death due to any cause (up to approximately 2.25 years)] ○ Percentage of participants who died among TC1/2/3 or IC1/2/3 subgroup of PP-ITT were reported. TC1 = presence of discernible programmed death-ligand 1 (PD-L1) staining of any intensity in >/=1% and <5% TCs; TC2: presence of discernible PD-L1 staining of any intensity in >/=5% and <50% TCs; TC3 = presence of discernible PD-L1 staining of any intensity in >/=50% TCs; IC1 = presence of discernible PD-L1 staining of any intensity in ICs covering between >/=1% and <5% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma; IC2 = presence of discernible PD-L1 staining of any intensity in ICs covering between >/=5% and <10% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma; IC3 = presence of discernible PD-L1 staining of any intensity in ICs covering >/=10% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma. 3. Overall Survival (OS): PP-ITT [Time Frame: Baseline until death due to any cause (up to approximately 2.25 years)] ○ OS duration is defined as the difference in time from the date of randomization to the date of death due to any cause. Data for participants who were not reported as having died at the time of analysis were censored at the date they were last known to be alive. Participants who had no post-baseline information were censored at the date of randomization plus 1 day. OS was estimated using KM methodology. 4. OS: TC1/2/3 or IC1/2/3 Subgroup of PP [Time Frame: Baseline until death due to any cause (up to approximately 2.25 years)] ○ OS duration is defined as the difference in time from the date of randomization to the date of death due to any cause. Data for participants who were not reported as having died at the time of analysis were censored at the date they were last known to be alive. Participants who had no post-baseline information were censored at the date of randomization plus 1 day. OS was estimated using KM methodology. 5. OS: SP-ITT [Time Frame: Baseline until death due to any cause (up to approximately 2.87 years)] ○ OS duration is defined as the difference in time from the date of randomization to the date of death due to any cause. Data for participants who were not reported as having died at the time of analysis were censored at the date they were last known to be alive. Participants who had no post-baseline information were censored at the date of randomization plus 1 day. OS was estimated using KM methodology. 6. OS: TC1/2/3 Or IC1/2/3 Subgroup of SP [Time Frame: Baseline until death from any cause (approximately 2.87 years)] ○ OS duration is defined as the difference in time from the date of randomization to the date of death due to any cause. Data for participants who were not reported as having died at the time of analysis were censored at the date they were last known to be alive. Participants who had no post-baseline information were censored at the date of randomization plus 1 day. OS was estimated using KM methodology.

7. OS: TC2/3 or IC2/3 Subgroup of SP [Time Frame: Baseline until death due to any cause (up to approximately 2.87 years)]
    - OS duration is defined as the difference in time from the date of randomization to the date of death due to any cause. Data for participants who were not reported as having died at the time of analysis were censored at the date they were last known to be alive. Participants who had no post-baseline information were censored at the date of randomization plus 1 day. OS was estimated using KM methodology.

8. OS: TC3 or IC3 Subgroup of SP [Time Frame: Baseline until death due to any cause (up to approximately 2.87 years)]
    - OS duration is defined as the difference in time from the date of randomization to the date of death due to any cause. Data for participants who were not reported as having died at the time of analysis were censored at the date they were last known to be alive. Participants who had no post-baseline information were censored at the date of randomization plus 1 day. OS was estimated using KM methodology.

Secondary endpoints

1. Percentage of Participants With Disease Progression (PD) as Determined by Investigator Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) or Death: PP-ITT [Time Frame: Baseline up to PD or Death (up to approximately 2.25 years)]
    - PD: at least 20% increase in the sum of diameters of target lesions compared to the smallest sum of diameters on-study and absolute increase of at least 5 millimeters (mm), or presence of new lesions.

2. Percentage of Participants With PD as Determined by Investigator Using RECIST v1.1 or Death: TC1/2/3 or IC1/2/3 Subgroup of PP [Time Frame: Baseline up to PD or Death (up to approximately 2.25 years)]
    - PD: at least 20% increase in the sum of diameters of target lesions compared to the smallest sum of diameters on-study and absolute increase of at least 5 mm, or presence of new lesions.

3. Progression-Free Survival (PFS) as Determined by Investigator Using RECIST v1.1: PP-ITT [Time Frame: Baseline up to PD or death due to any cause, whichever occurred first (up to approximately 2.25 years)]
    - PFS is defined as the time between the date of randomization and the date of first documented PD or death, whichever occurs first. Participants who are alive and have not experienced PD at the time of analysis were censored at the time of the last tumor assessment. Participants with no post-baseline tumor assessment were censored at the randomization date plus 1 day. PD: at least 20% increase in the sum of diameters of target lesions compared to the smallest sum of diameters on-study and absolute increase of at least 5 mm, or presence of new lesions.

4. PFS as Determined by Investigator Using RECIST v1.1: TC1/2/3 or IC1/2/3 Subgroup of PP [Time Frame: Baseline up to PD or death due to any cause, whichever occurred first (up to approximately 2.25 years)]
    - PFS is defined as the time between the date of randomization and the date of first documented PD or death, whichever occurs first. Participants who are alive and have not experienced PD at the time of analysis were censored at the time of the last tumor assessment. Participants with no post-baseline tumor assessment were censored at the randomization date plus 1 day. PD: at least 20% increase in the sum of diameters of target lesions compared to the smallest sum of diameters on-study and absolute increase of at least 5 mm, or presence of new lesions.

	5. Percentage of Participants With Objective Response as Determined Using RECIST v1.1: PP-ITT [Time Frame: Baseline up to PD or death due to any cause, whichever occurred first (up to approximately 2.25 years)] ○ Objective response is defined as a complete response (CR) or partial response (PR) as determined by the Investigator using RECIST v1.1 on 2 consecutive occasions at least 6 weeks apart. CR was defined as complete disappearance of all target lesions and non-target disease, with the exception of nodal disease. All nodes, both target and non-target, must decrease to normal (short axis less than [<] 10 mm). No new lesions. At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR. No new lesions. 6. Percentage of Participants With Objective Response as Determined Using RECIST v1.1: TC1/2/3 or IC1/2/3 Subgroup of PP [Time Frame: Baseline up to PD or death due to any cause, whichever occurred first (up to approximately 2.25 years)] ○ Objective response is defined as a CR or PR as determined by the Investigator using RECIST v1.1 on 2 consecutive occasions at least 6 weeks apart. CR was defined as complete disappearance of all target lesions and non-target disease, with the exception of nodal disease. All nodes, both target and non-target, must decrease to normal (short axis <10 mm). No new lesions. At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR. No new lesions. 7. Duration of Response (DOR) as Determined by Investigator Using RECIST v1.1: PP-ITT [Time Frame: From first objective response of CR or PR to PD or death due to any cause, whichever occurred first (up to approximately 2.25 years)] ○ DOR:Duration from the first tumor assessment that supports the participant's objective response to PD or death due to any cause,whichever occurs first.CR:complete disappearance of all target lesions and non-target disease.All nodes,both target and non-target,must decrease to normal. No new lesions.PR: At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR.Participants who have not experienced PD at the time of analysis were censored at the time of the last tumor assessment.Participants with no post-baseline tumor assessment were censored at the randomization date plus 1 day.PD:at least 20% increase in the sum of diameters of target lesions compared to the smallest sum of diameters on-study and absolute increase of at least 5 mm,progression of existing non-target lesions,or presence of new lesions.DOR was estimated using KM methodology. 8. DOR as Determined by Investigator Using RECIST v1.1: TC1/2/3 or IC1/2/3 Subgroup of PP [Time Frame: From first objective response of CR or PR to PD or death due to any cause, whichever occurred first (up to approximately 2.25 years)] ○ DOR:Duration from the first tumor assessment that supports the participant's objective response to PD or death due to any cause,whichever occurs first.CR:complete disappearance of all target lesions and non-target disease.All nodes,both target and non-target,must decrease to normal. No new lesions.PR: At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR.Participants who have not experienced PD at the time of analysis were censored at the time of the last tumor assessment.Participants with no post-baseline tumor assessment were censored at the randomization date plus 1 day.PD:at least 20% increase in the sum of diameters of target lesions compared to the smallest sum of diameters on-study and absolute increase of at least 5 mm,progression of

existing non-target lesions,or presence of new lesions.DOR was estimated using KM methodology.

9. Percentage of Participants With Anti-Therapeutic Antibodies (ATAs) Against Atezolizumab [Time Frame: Baseline up to approximately 2.25 years (assessed at predose [Hour {Hr} 0] on Day 1 of Cycles 1, 2, 3, 4, 8, 16, then every 8 cycles up to end of treatment (EOT) [approximately 2.25 years]; 120 days after EOT [approximately 2.25 years] [1 Cycle=21 days])]

10. Maximum Observed Serum Atezolizumab Concentration (Cmax) [Time Frame: Predose (Hr 0), 30 minutes (min) post-infusion (infusion duration: 60 min) on Cycle 1 Day 1 (1 Cycle=21 days)]

11. Minimum Observed Serum Atezolizumab Concentration (Cmin) [Time Frame: Predose (Hr 0) on Day 1 of Cycles 1, 2, 3, 4, 8, 16, 24, 32, EOT (approximately 2.25 years); 120 days after EOT (approximately 2.25 years) (1 Cycle=21 days)]

12. Time to Deterioration (TTD) in Patient-Reported Lung Cancer Symptoms, Using the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ) Lung Cancer Supplemental Module 13 (LC13) [Time Frame: Day 1 of each treatment Cycle up to EOT (up to approximately 2.25 years) (1 Cycle = 21 days)]
    - TTD in patient-reported lung cancer symptoms (pain in chest or in arm/shoulder, dyspnea, or cough) was a composite endpoint defined as the time from randomization to the earliest time the participant's scale scores showed a 10 point or greater increase after baseline in any of the symptoms. A >/=10-point change in the score perceived by participants was considered as clinically significant. The QLQ-LC13 consisted of 1 multi-item scale and 9 single items that assessed the specific symptoms (dyspnea, cough, hemoptysis, and site specific pain), side effects (sore mouth, dysphagia, neuropathy, and alopecia), and pain medication use of lung cancer participants receiving chemotherapy. Scale score range: 0 to 100. Higher symptom score = greater degree of symptom severity.

13. EORTC QLQ Core 30 (C30) Questionnaire Score: Single Items [Time Frame: Day 1 of each treatment Cycle up to EOT (up to approximately 2.25 years); 6 week following PD (Pro Week 6 Pd) (up to approximately 2.25 years); survival follow-up-1 (up to approximately 2.25 years) (1 Cycle= 21 days)]
    - EORTC QLQ-C30 included global health status (GHS)/quality of life (QOL), functional scales (physical, role, cognitive, emotional, social), symptom scales (fatigue, pain, nausea/vomiting), and single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, financial difficulties). Most questions from QLQ-C30 were a 4-point scale (1/Not at All to 4/Very Much), except Items 29-30, which comprise GHS scale and were a 7-point scale (1/Very Poor to 7/Excellent). For this instrument, GHS/QOL and functional scales were linearly transformed so each score ranged 0-100, where lower scores indicate poorer functioning (e.g., worsening) and higher scores indicate better functioning (e.g., improvement). Symptom scales/items were also linearly transformed so each score ranged 0-100, where higher scores indicate worse symptoms (e.g., more severe/worsened) and lower scores indicate less symptoms (e.g., less severe/improvement).

14. EORTC QLQ-C30 Questionnaire Score: Functional Subscales [Time Frame: Day 1 of each treatment Cycle up to EOT (up to approximately 2.25 years); 6 week following PD (Pro Week 6 Pd) (up to approximately 2.25 years); survival follow-up-1 (up to approximately 2.25 years) (1 Cycle= 21 days)]
    - EORTC QLQ-C30 included GHS/QOL, functional scales (physical, role, cognitive, emotional, social), symptom scales (fatigue, pain, nausea/vomiting), and single items (dyspnea, appetite loss, insomnia,

	constipation, diarrhea, financial difficulties). Most questions from QLQ-C30 were a 4-point scale (1/Not at All to 4/Very Much), except Items 29-30, which comprise GHS scale and were a 7-point scale (1/Very Poor to 7/Excellent). For this instrument, GHS/QOL and functional scales were linearly transformed so each score ranged 0-100, where lower scores indicate poorer functioning (e.g., worsening) and higher scores indicate better functioning (e.g., improvement). Symptom scales/items were also linearly transformed so each score ranged 0-100, where higher scores indicate worse symptoms (e.g., more severe/worsened) and lower scores indicate less symptoms (e.g., less severe/improvement). 15. EORTC QLQ-C30 Questionnaire Score: GHS Scale [Time Frame: Day 1 of each treatment Cycle up to EOT (up to approximately 2.25 years); 6 week following PD (Pro Week 6 Pd) (up to approximately 2.25 years); survival follow-up-1 (up to approximately 2.25 years) (1 Cycle= 21 days)] o EORTC QLQ-C30 included GHS/QOL, functional scales (physical, role, cognitive, emotional, social), symptom scales (fatigue, pain, nausea/vomiting), and single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, financial difficulties). Most questions from QLQ-C30 were a 4-point scale (1/Not at All to 4/Very Much), except Items 29-30, which comprise GHS scale and were a 7-point scale (1/Very Poor to 7/Excellent). For this instrument, GHS/QOL and functional scales were linearly transformed so each score ranged 0-100, where lower scores indicate poorer functioning (e.g., worsening) and higher scores indicate better functioning (e.g., improvement). Symptom scales/items were also linearly transformed so each score ranged 0-100, where higher scores indicate worse symptoms (e.g., more severe/worsened) and lower scores indicate less symptoms (e.g., less severe/improvement). 16. EORTC QLQ-C30 Questionnaire Score: Symptom Subscale [Time Frame: Day 1 of each treatment Cycle up to EOT (up to approximately 2.25 years); 6 week following PD (Pro Week 6 Pd) (up to approximately 2.25 years); survival follow-up-1 (up to approximately 2.25 years) (1 Cycle= 21 days)] o EORTC QLQ-C30 included GHS/QOL, functional scales (physical, role, cognitive, emotional, social), symptom scales (fatigue, pain, nausea/vomiting), and single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, financial difficulties). Most questions from QLQ-C30 were a 4-point scale (1/Not at All to 4/Very Much), except Items 29-30, which comprise GHS scale and were a 7-point scale (1/Very Poor to 7/Excellent). For this instrument, GHS/QOL and functional scales were linearly transformed so each score ranged 0-100, where lower scores indicate poorer functioning (e.g., worsening) and higher scores indicate better functioning (e.g., improvement). Symptom scales/items were also linearly transformed so each score ranged 0-100, where higher scores indicate worse symptoms (e.g., more severe/worsened) and lower scores indicate less symptoms (e.g., less severe/improvement). 17. EORTC QLQ-LC13 Questionnaire Score: Alopecia [Time Frame: Day 1 of each treatment Cycle up to EOT (up to approximately 2.25 years); 6 week following PD (Pro Week 6 Pd) (up to approximately 2.25 years); survival follow-up-1 (up to approximately 2.25 years) (1 Cycle= 21 days)] o QLQ-LC13 consisted of 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy experienced during past 1 week. The 13 questions comprised 1 multi-item scale for dyspnea and 10 single-item symptoms and side effects (coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder, pain in other parts. Response range: (1) not at all to (4) very much. Scores for

	each item were transformed to 0 to 100, where higher symptom score = greater degree of symptoms. Results have been reported for alopecia. 18. EORTC QLQ-LC13 Questionnaire Score: Coughing [Time Frame: Day 1 of each treatment Cycle up to EOT (up to approximately 2.25 years); 6 week following PD (Pro Week 6 Pd) (up to approximately 2.25 years); survival follow-up-1 (up to approximately 2.25 years) (1 Cycle= 21 days)] o QLQ-LC13 consisted of 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy experienced during past 1 week. The 13 questions comprised 1 multi-item scale for dyspnea and 10 single-item symptoms and side effects (coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder, pain in other parts. Response range: (1) not at all to (4) very much. Scores for each item were transformed to 0 to 100, where higher symptom score = greater degree of symptoms. Results have been reported for coughing. 19. EORTC QLQ-LC13 Questionnaire Score: Dysphagia [Time Frame: Day 1 of each treatment Cycle up to EOT (up to approximately 2.25 years); 6 week following PD (Pro Week 6 Pd) (up to approximately 2.25 years); survival follow-up-1 (up to approximately 2.25 years) (1 Cycle= 21 days)] o QLQ-LC13 consisted of 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy experienced during past 1 week. The 13 questions comprised 1 multi-item scale for dyspnea and 10 single-item symptoms and side effects (coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder, pain in other parts. Response range: (1) not at all to (4) very much. Scores for each item were transformed to 0 to 100, where higher symptom score = greater degree of symptoms. Results have been reported for dysphagia. 20. EORTC QLQ-LC13 Questionnaire Score: Dyspnea [Time Frame: Day 1 of each treatment Cycle up to EOT (up to approximately 2.25 years); 6 week following PD (Pro Week 6 Pd) (up to approximately 2.25 years); survival follow-up-1 (up to approximately 2.25 years) (1 Cycle= 21 days)] o QLQ-LC13 consisted of 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy experienced during past 1 week. The 13 questions comprised 1 multi-item scale for dyspnea and 10 single-item symptoms and side effects (coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder, pain in other parts. Response range: (1) not at all to (4) very much. Scores for each item were transformed to 0 to 100, where higher symptom score = greater degree of symptoms. Results have been reported for dyspnea. 21. EORTC QLQ-LC13 Questionnaire Score: Hemoptysis [Time Frame: Day 1 of each treatment Cycle up to EOT (up to approximately 2.25 years); 6 week following PD (Pro Week 6 Pd) (up to approximately 2.25 years); survival follow-up-1 (up to approximately 2.25 years) (1 Cycle= 21 days)] o QLQ-LC13 consisted of 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy experienced during past 1 week. The 13 questions comprised 1 multi-item scale for dyspnea and 10 single-item symptoms and side effects (coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder, pain in other parts. Response range: (1) not at all to (4) very much. Scores for each item were transformed to 0 to 100, where higher symptom score = greater degree of symptoms. Results have been reported for hemoptysis.

22. EORTC QLQ-LC13 Questionnaire Score: Pain in Arm or Shoulder [Time Frame: Day 1 of each treatment Cycle up to EOT (up to approximately 2.25 years); 6 week following PD (up to approximately 2.25 years); survival follow-up-1 (up to approximately 2.25 years) (1 Cycle= 21 days)]
    - QLQ-LC13 consisted of 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy experienced during past 1 week. The 13 questions comprised 1 multi-item scale for dyspnea and 10 single-item symptoms and side effects (coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder, pain in other parts. Response range: (1) not at all to (4) very much. Scores for each item were transformed to 0 to 100, where higher symptom score = greater degree of symptoms. Results have been reported for pain in arm or shoulder.

23. EORTC QLQ-LC13 Questionnaire Score: Pain in Chest [Time Frame: Day 1 of each treatment Cycle up to EOT (up to approximately 2.25 years); 6 week following PD (up to approximately 2.25 years); survival follow-up-1 (up to approximately 2.25 years) (1 Cycle= 21 days)]
    - QLQ-LC13 consisted of 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy experienced during past 1 week. The 13 questions comprised 1 multi-item scale for dyspnea and 10 single-item symptoms and side effects (coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder, pain in other parts. Response range: (1) not at all to (4) very much. Scores for each item were transformed to 0 to 100, where higher symptom score = greater degree of symptoms. Results have been reported for pain in chest.

24. EORTC QLQ-LC13 Questionnaire Score: Peripheral Neuropathy [Time Frame: Day 1 of each treatment Cycle up to EOT (up to approximately 2.25 years); 6 week following PD (up to approximately 2.25 years); survival follow-up-1 (up to approximately 2.25 years) (1 Cycle= 21 days)]
    - QLQ-LC13 consisted of 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy experienced during past 1 week. The 13 questions comprised 1 multi-item scale for dyspnea and 10 single-item symptoms and side effects (coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder, pain in other parts. Response range: (1) not at all to (4) very much. Scores for each item were transformed to 0 to 100, where higher symptom score = greater degree of symptoms. Results have been reported for peripheral neuropathy.

25. EORTC QLQ-LC13 Questionnaire Score: Pain in Other Parts [Time Frame: Day 1 of each treatment Cycle up to EOT (up to approximately 2.25 years); 6 week following PD (up to approximately 2.25 years); survival follow-up-1 (up to approximately 2.25 years) (1 Cycle= 21 days)]
    - QLQ-LC13 consisted of 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy experienced during past 1 week. The 13 questions comprised 1 multi-item scale for dyspnea and 10 single-item symptoms and side effects (coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder, pain in other parts. Response range: (1) not at all to (4) very much. Scores for each item were transformed to 0 to 100, where higher symptom score = greater degree of symptoms. Results have been reported for pain in other parts.

26. EORTC QLQ-LC13 Questionnaire Score: Sore Mouth [Time Frame: Day 1 of each treatment Cycle up to EOT (up to approximately 2.25 years); 6 week following PD (up to approximately 2.25 years); survival follow-up-1 (up to approximately 2.25 years) (1 Cycle= 21 days)]
    - QLQ-LC13 consisted of 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy experienced during past 1 week. The 13 questions comprised 1 multi-item scale for dyspnea and 10 single-item symptoms and side effects (coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder, pain in other parts. Response range: (1) not at all to (4) very much. Scores for each item were transformed to 0 to 100, where higher symptom score = greater degree of symptoms. Results have been reported for sore mouth.

27. PFS as Determined by Investigator Using RECIST v1.1: SP-ITT [Time Frame: Baseline up to PD or death due to any cause, whichever occurred first (up to approximately 2.87 years)]
    - PFS is defined as the time between the date of randomization and the date of first documented PD or death, whichever occurs first. Participants who are alive and have not experienced PD at the time of analysis were censored at the time of the last tumor assessment. Participants with no post-baseline tumor assessment were censored at the randomization date plus 1 day. PD: at least 20% increase in the sum of diameters of target lesions compared to the smallest sum of diameters on-study and absolute increase of at least 5 mm, or presence of new lesions.

28. Percentage of Participants With Objective Response as Determined Using RECIST v1.1: SP-ITT [Time Frame: Baseline up to PD or death due to any cause, whichever occurred first (up to approximately 2.87 years)]
    - Objective response is defined as a complete response (CR) or partial response (PR) as determined by the Investigator using RECIST v1.1 on 2 consecutive occasions at least 6 weeks apart. CR was defined as complete disappearance of all target lesions and non-target disease, with the exception of nodal disease. All nodes, both target and non-target, must decrease to normal (short axis less than [<] 10 mm). No new lesions. At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR. No new lesions.

29. DOR as Determined by Investigator Using RECIST v1.1: SP ITT [Time Frame: From first objective response of CR or PR to PD or death due to any cause, whichever occurred first (up to approximately 2.87 years)]
    - DOR:Duration from the first tumor assessment that supports the participant's objective response to PD or death due to any cause,whichever occurs first.CR:complete disappearance of all target lesions and non-target disease.All nodes,both target and non-target,must decrease to normal. No new lesions.PR: At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR.Participants who have not experienced PD at the time of analysis were censored at the time of the last tumor assessment.Participants with no post-baseline tumor assessment were censored at the randomization date plus 1 day.PD:at least 20% increase in the sum of diameters of target lesions compared to the smallest sum of diameters on-study and absolute increase of at least 5 mm,progression of existing non-target lesions,or presence of new lesions.DOR was estimated using KM methodology.

Trial name: OAK	NCT number: 02008227
Method of analysis	Overall survival was compared between treatment groups with a stratified log-rank test at the two-sided significance level. The Kaplan-Meier approach was used to estimate the median overall survival; the Brookmeyer-Crowley methodology was used to estimate 95% CIs. The HR was estimated with a stratified Cox regression analysis. Stratification factors were the same used for randomization. Patients not reported as having died at the time of analysis were censored at the date they were last known to be alive. Patients without post-baseline information were censored at the randomisation date plus 1 day. Progression-free survival and duration of response were analysed with the same methods as the overall survival analysis. The proportion of patients with an objective response and the corresponding 95% CIs for each treatment group were calculated with the Clopper-Pearson method and compared between treatment groups with the Cochran–Mantel–Haenszel test.
Subgroup analyses	Prespecified analyses were done to determine the consistency of the treatment effect according to key baseline characteristics and in different subgroups of patients according to their tumour PD-L1 expression level. Given the exploratory nature of subgroup analyses and potential small sample sizes in specific subgroups, the HRs from these analyses were estimated with an unstratified Cox regression analysis.
Subgroup analyses	N/A

Abbreviations are explained in the text. Study is used in the health economic model only. Information source: [40,88]

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 44: Baseline characteristics of patients in the study included for the comparative analysis of efficacy and safety

	IMpower010					
	ITT group [19,27]		PL-L1 ≥50% group [27]		PL-L1 ≥50% group excl. EGFR/ALK+ [28]	
	ATZ (n=507)	BSC (n=498)	ATZ (n=115)	BSC (n=114)	ATZ (n=106)	BSC (n=103)
Age, years — median (IQR)	62 (57–67)	62 (56–68)	62 (34–77)	62 (36–84)	62 (34-77)	62 (36-84)
Age group — n (%)						
<65 years	323 (63.7)	300 (60.2)	70 (60.9)	68 (59.6)	65 (61.3)	62 (60.2)
≥65 years	184 (36.3)	198 (39.8)	45 (39.1)	46 (40.4)	41 (38.7)	41 (39.8)

Sex — n (%)						
Male	337 (66.5)	335 (67.3)	89 (77.4)	78 (68.4)	84 (79.2)	73 (70.9)
Female	170 (33.5)	163 (32.7)	26 (22.6)	36 (31.6)	22 (20.8)	30 (29.1)
Race — n (%)						
White	362 (71.4)	376 (75.5)	75 (65.2)	86 (75.4)	71 (67.0)	77 (74.8)
Asian	130 (25.6)	112 (22.5)	36 (31.3)	26 (22.8)	31 (29.2)	24 (23.3)
Other	15 (3.0)	10 (2.0)	4 (3.5)	2 (1.8)	4 (3.8)	2 (1.9)
ECOG performance status* — n (%)						
0	273 (53.8)	283 (56.8)	71 (61.7)	60 (52.6)	66 (62.3)	53 (51.5)
1	232 (45.8)	214 (43.0)	44 (38.3)	53 (46.5)	40 (37.7)	49 (47.6)
2	2 (<1)	1 (<1)	0	1 (<1)	0 (0)	1 (1.0)
Histology — n (%)						
Squamous	179 (35.3)	167 (33.5)	47 (40.9)	45 (39.5)	47 (44.3)	45 (43.7)
Non-squamous	328 (64.7)	331 (66.5)	68 (59.1)	69 (60.5)	59 (55.7)	58 (56.3)
Tobacco use history — n (%)						
Never	114 (22.5)	108 (21.7)	16 (13.9)	15 (13.2)	11 (10.4)	10 (9.7)
Current/previous	393 (77.5)	390 (78.3)	99 (86.1)	99 (86.8)	95 (89.6)	93 (90.3)
Previous	317 (62.5)	304 (61.0)	83 (72.2)	77 (67.5)	79 (74.5)	72 (69.9)

Current	76 (15.0)	86 (17.3)	16 (13.9)	22 (19.3)	16 (15.1)	21 (20.4)
Stage — n (%)						
IB	65 (12.8)	58 (11.6)	-	-	-	-
IIA	147 (29.0)	148 (29.7)	35 (30.4)	41 (36.0)	31 (29.2)	33 (32.0)
IIB	90 (17.8)	84 (16.9)	27 (23.5)	16 (14.0)	27 (25.5)	15 (14.6)
IIIA	205 (40.4)	208 (41.8)	53 (46.1)	57 (50.0)	48 (45.3)	55 (53.4)
Type of surgery — n (%)						
Lobectomy	394 (77.7)	391 (78.5)	85 (73.9)	85 (74.6)	76 (71.7)	74 (71.8)
Sleeve lobectomy	4 (<1)	4 (<1)	2 (1.7)	1 (0.9)	2 (1.9)	1 (1.0)
Bilobectomy	31 (6.1)	19 (3.8)	7 (6.1)	7 (6.1)	7 (6.6)	7 (6.8)
Pneumonectomy	77 (15.2)	83 (16.7)	20 (17.4)	20 (17.5)	20 (18.9)	20 (19.4)
Other	1 (<1)	1 (<1)	1 (0.9)	1 (0.9)	1 (1.0)	1 (1.0)
EGFR mutation status† — n (%)						
Positive	53 (10.5)	64 (12.9)	6 (5.2)	8 (7.0)	-	-
Negative	261 (51.5)	266 (53.4)	60 (52.2)	64 (56.1)	57 (53.8)	61 (59.2)
Unknown	193 (38.0)	168 (33.7)	49 (42.6)	42 (36.8)	49 (46.2)	42 (40.8)
ALK rearrangement status†						
Positive	15 (3.0)	18 (3.6)	3 (2.6)	3 (2.6)	-	-

Negative	280 (55.2)	294 (59.0)	62 (53.9)	62 (54.4)	56 (52.8)	55 (53.4)
Unknown	212 (41.8)	186 (37.3)	50 (43.5)	49 (43.0)	50 (47.2)	48 (46.6)
PD-L1 status by SP263‡ — n (%)						
<1%	210 (41.4)	234 (47.0)	NA	NA	NA	NA
≥1%	283 (55.8)	252 (50.6)	NA	NA	NA	NA
≥50%	131 (26.6)	127 (26.1)	115 (100)	114 (100)	106 (100)	103 (100)

*At randomisation; patients with ECOG performance status 2 had protocol deviations. †Assessed locally or centrally for patients with non-squamous NSCLC. 89% of patients with unknown EGFR status and 81% of patients with unknown ALK status in the intention-to-treat population had squamous NSCLC and were not required to undergo local or central testing. ‡26 patients in the intention-to-treat population (14 in the atezolizumab group and 12 in the best supportive care group) had unknown PD-L1 status as assessed by SP263. §PD-L1 expression on TC or IC was scored as: TC0/1 and IC0/1 was <5% TC and IC; TC0/1 and IC2/3 was <5% TC and ≥5% IC; TC2/3 and any IC was ≥5% TC and any IC status. Abbreviations: ALK - anaplastic lymphoma kinase; ATZ – atezolizumab; BSC – best supportive care; EGFR - epidermal growth factor receptor; PD-L1 - programmed death-ligand 1.

Comparability of patients across studies

The median age of all randomised patients was 62 years (range: 26–84 years), and the majority of patients were male (66.9%); had an ECOG PS score of 0 (55.3%), non-squamous histology (65.6%), and stage IIIA disease (41.1%); were current or previous smokers (77.9%); and had tumours with PD-L1 expression on ≥1% of TCs (SP263 IHC, 54.6%). The proportion of patients with NSCLC stage IB was similar among atezolizumab and BSC patient cohorts in the ITT population.

In general, similar baseline characteristics were observed in the subpopulation with PD-L1 TC ≥50% without EGFR/ALK+. Key characteristics such as non-squamous histology were consistent between atezolizumab- and BSC-treated patients. For other characteristics, small differences were observed between treatment arms. In the atezolizumab arm there was a higher proportion of males, and a lower proportion of patients of white race and a higher proportion of patients of Asian race compared to the BSC arm. However, differences in sex and race are not expected to influence the outcomes in the study. Small difference was also observed for ECOG PS and stage. There was a higher proportion of patients in ECOG PS 0 in the atezolizumab arm compared to BSC, thus patients have a slightly better performance status in the atezolizumab arm. In terms of stage, there was a slightly lower proportion of patients with stage IIA, a higher proportion of patients with stage IIB, and a slightly lower proportion of patients with IIIA, making it difficult to determine whether the overall patient prognosis in either arm is better than the other. Overall, the observed differences between treatment arms are small and are not expected to affect the outcomes to a significant degree.

Comparability of the study populations with Danish patients eligible for treatment

The target population for adjuvant treatment with atezolizumab are patients with NSCLC whose tumours have PD-L1 expression on ≥50% of TCs and who have undergone resection and received platinum-based chemotherapy and do not have EGFR mutations or ALK rearrangements. This is based on the available data from the IMpower010 study, which shows that the treatment effect is largely driven by patients with high PD-L1 expression although the study did include all patients with >1% PD-L1 expression. Data and demographics from the PD-L1 high early NSCLC population are not available in a registry setting in Denmark but the comparability has been discussed with Danish experts.

In Denmark the use of adjuvant treatment is described in the guideline by DLCG [6]. The purpose of this guideline is to ensure that patients going through surgery and where the staging indicates oncological treatment are being referred and assessed in relation to adjuvant chemotherapy. The guideline does not state relevant age etc. Data from a Danish cohort of patients reports a median DFS of 37.8 months (32.6-51.1 months) for stage IB-III NSCLC patients undergoing surgery, which corresponds nicely to the results observed in the BSC arm of IMpower010. The Danish data have been presented at the WCLC on August 6-9, 2022 [89].

According to expert opinion the study population in IMpower010 is comparable to a potential future Danish population but age, PD-L1 expression and type of surgery are discussed below.

Age

Median age in IMpower010 is assessed to be a bit lower than the Danish population. But this is not assessed to be an important prognostic variable. The median age of patients receiving adjuvant chemotherapy in Denmark is not stated in the yearly report by DLCG and DLCR [3]. Based on discussion with experts, the characteristics of the expected patient groups are described below.

Relevant patient age for treatment with adjuvant immunotherapy:

- Patients younger than 70 years with a good performance status (ECOG 0-1)
- Biologically young patients above 70 years should be evaluated for treatment

In the current guideline for adjuvant treatment it is stated that it should be assessed if the patient is eligible for adjuvant treatment based on the patient's general condition and comorbidities. This to ensure that the patient can withstand the treatment [6].

PD-L1 expression

The PD-L1 expression in a Danish consecutive study population including all patients with a new diagnosis of NSCLC in The Capital Region of Denmark from 1st of February 2018 to 30th November 2018 was published in 2020 [13]. Here it was reported that 25% of the stage II patients and 28% of the stage III patients had a PD-L1 expression ≥50% (using 22C3 antibody). This is the same level as reported in the IMpower010 study for stage II (using SP263 antibody).

Surgery

In 2021, 83% of the surgeries performed in Denmark were lobectomies [3] making this the far most frequent surgery as it is the case in IMpower010. According to experts, adjuvant therapy is not effective after pneumonectomy and the rate of pneumonectomy is at 2% in Denmark in 2021 [3]. The rate of pneumonectomy is therefore higher in IMpower010 but as the efficacy is assessed to be poor after pneumonectomy the difference will not have a negative impact in connection to a potential implementation of adjuvant atezolizumab treatment in Denmark.

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Table 45: Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
DFS	DFS is defined as the time from randomisation to the date of first documented recurrence of NSCLC (as determined by the investigator after an integrated assessment of radiographic data, biopsy sample results (if available), and clinical status), occurrence of new primary NSCLC (as assessed by investigator), or death from any cause, whichever occurred first.	DFS is a commonly used endpoint within oncology trials. It is used to assess the time during which patients are alive without disease recurrence or occurrence of new primary disease. DFS is not affected by the impact of subsequent treatment and patient crossover between trial arms in the same manner as OS, and therefore serves as a relevant supplement to OS.	To our knowledge, published information on minimal important differences is not available.
OS	OS is defined as the time from randomisation to death of any cause. All randomised patients were followed every 3 months until death, loss to follow-up, withdrawal of study consent, or study termination by the sponsor, whichever occurred first, to determine OS.	OS is considered an important clinical endpoint in clinical trials within oncology. For many years it has been considered the gold-standard endpoint for establishing clinical benefit. However, using OS can be associated with certain limitations as it may be affected by subsequent therapy or patient crossover between treatment arms in studies of early treatment.	To our knowledge, published information on minimal important differences is not available.

Outcome measure	Definition	Validity	Clinical relevance
Grade 3-4 AEs	Proportion of patients that experience any grade 3-4 AEs. AEs are coded using the standard MedDRA and grouped system organ class. Grading (severity of the AE) is defined according to Common Terminology Criteria for Adverse Events (CTCAE) version 4 (NCI CTCAE v4.0).	The proportion of patients that experience grade ≥3 adverse events is an expression of possible severe toxicity. Adverse events are not necessarily related to treatment. In previous Medicines Council assessments within NSCLC, grade 3-4 AEs has been defined as an important clinical endpoint.	To our knowledge, published information on minimal important differences is not available.
SAEs	Proportion of patients that experience any serious AEs.		To our knowledge, published information on minimal important differences is not available.
Discontinuation due to AEs	Proportion of patients that discontinue study treatment due to any AE. AEs are coded using the standard MedDRA and grouped system organ class.	In previous Medicines Council assessments within NSCLC, discontinuation due to AEs has been defined as one of the most important clinical endpoints.	To our knowledge, published information on minimal important differences is not available.

Abbreviations: AE – adverse event; CTCAE - Common Terminology Criteria for Adverse Events; DFS – disease-free survival; NSCLC – non-small cell lung cancer; OS – overall survival; SAE – serious adverse event.

Results per study

Table 46: Results of IMpower010 (NCT02486718) - PD-L1 ≥50%, excl. EGFR/ALK+

	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 DFS	ATZ	106	NE (NE-NE)	NE	NE	NE	HR: 0.44	0.27-0.71	0.0007	HR was estimated by a Cox regression model, including two-sided 95% CIs. The unstratified HR is presented here. Treatment comparisons were based on the log-rank test. Median DFS was estimated by Kaplan-Meier methodology, and the Brookmeyer-Crowley method was used to establish the 95% CIs.	CCOD: Jan 21, 2021. Median follow-up: 34.2 mo. [27]
	BSC	103	37.3 (30.1-NE)								
DFS rate at 3 years	ATZ	106	75.1% (65.4-84.8)	24.7%	9.8-39.5	0.011	N/A	N/A	N/A	3-year landmark DFS rate was estimated by Kaplan-Meier methodology, and the Greenwood's formula were used to establish the 95% CIs.	CCOD: Jan 21, 2021. Median follow-up: 34.2 mo. [8,27]
	BSC	103	50.4% (39.2-61.7)								
DFS rate at 5 years	ATZ	106	NE (NE-NE)	NE	NE	NE	N/A	N/A	N/A	5-year landmark DFS rate was estimated by Kaplan-Meier methodology, and the Greenwood's formula were used to establish the 95% CIs.	CCOD: Jan 21, 2021. Median follow-up: 34.2 mo. [27]
	BSC	103	NE (NE-NE)								
Median OS	ATZ	106	NE (NE-NE)	NE	NE	NE	HR: 0.42	0.23-0.78	0.01		CCOD: Apr 18, 2022. Median

	BSC	103	NE (NE-NE)							Same methodology as applied for DFS. The unstratified HR is presented here.	follow-up: 47.7 mo. [31]
OS rate at 3 years	ATZ	106	89.1% (83.1- 95.2)	11.6%	1.4-22.0	0.0263	N/A	N/A	N/A	Same methodology as applied for DFS.	CCOD: Apr 18, 2022. Median follow-up: 47.7 mo. [28]
	BSC	103	77.5% (69.2-85.8)								
OS rate at 5 years	ATZ	106	84.8% (77.7-91.9)	17.3%	5.0-29.6	0.0059	N/A	N/A	N/A	Same methodology as applied for DFS.	CCOD: Apr 18, 2022. Median follow-up: 47.7 mo. [28]
	BSC	103	67.5% (57.5-77.6)								

Abbreviations: ALK - anaplastic lymphoma kinase; ATZ – atezolizumab; BSC – best supportive care; CCOD – clinical cutoff date; CI – confidence interval; DFS – disease-free survival; EGFR - epidermal growth factor receptor; HR – hazard ratio; N – number of patients; N/A - not applicable; OS – overall survival; PD-L1 - programmed death-ligand 1.

Table 47: Safety results of IMpower010 (NCT02486718) - Safety population

				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**		
Grade 3-4 AEs Safety population	ATZ	495	108 (21.8%)	10.3%	N/A	N/A	N/A	N/A	N/A	Safety was analysed in the safety population, defined as all patients randomly assigned who received atezolizumab or best supportive care.	CCOD: Jan 21, 2021 [19]
	BSC	495	57 (11.5%)								

Grade 3-4 TRAEs Safety population	ATZ	495	53 (10.7%)	10.7%	N/A	N/A	N/A	N/A	N/A	Safety was analysed in the safety population, defined as all patients randomly assigned who received atezolizumab or best supportive care.	CCOD: Jan 21, 2021 [8,27]
	BSC	495	0 (0%)								
SAEs Safety population	ATZ	495	87 (17.6%)	9.1%	N/A	N/A	N/A	N/A	N/A	Safety was analysed in the safety population, defined as all patients randomly assigned who received atezolizumab or best supportive care.	CCOD: Jan 21, 2021 [19]
	BSC	495	42 (8.5%)								
TR-SAEs Safety population	ATZ	495	37 (7.5%)	7.5%	N/A	N/A	N/A	N/A	N/A	Safety was analysed in the safety population, defined as all patients randomly assigned who received atezolizumab or best supportive care.	CCOD: Jan 21, 2021 [8,27]
	BSC	495	0 (0%)								
Discontinuation due to AEs Safety population	ATZ	495	90 (18.2%)	N/A	N/A	N/A	N/A	N/A	N/A	Safety was analysed in the safety population, defined as all patients randomly assigned who received atezolizumab or best supportive care.	CCOD: Jan 21, 2021 [19]
	BSC	495	N/A								

Abbreviations: AE – adverse event; ATZ – atezolizumab; BSC – best supportive care; CCOD – clinical cutoff date; CI – confidence interval; N – number of patients; N/A - not applicable; SAE – serious adverse event; TRAE – treatment-related AE; TR-SAE – treatment-related serious adverse event.

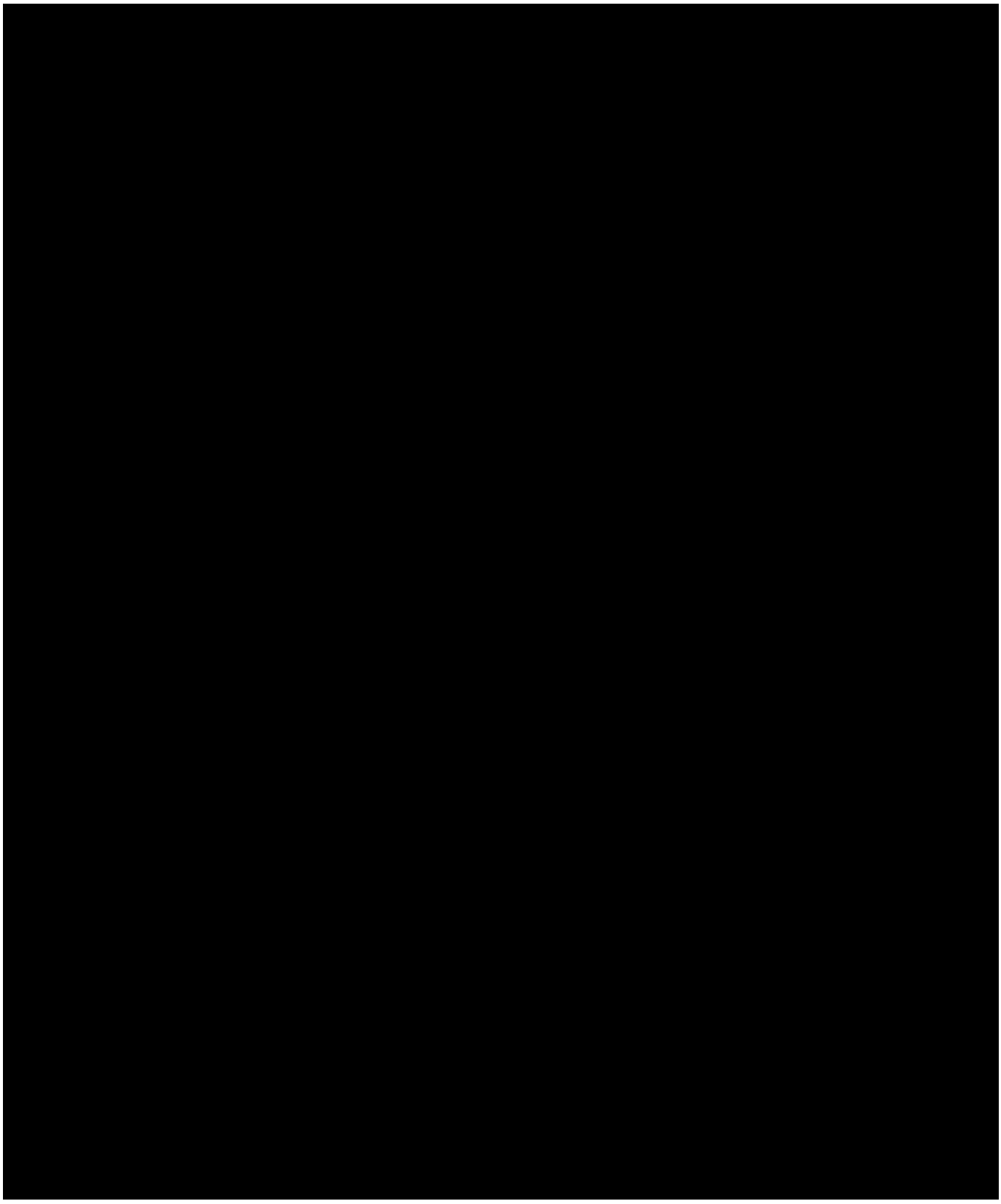
Appendix E Safety data for intervention and comparator

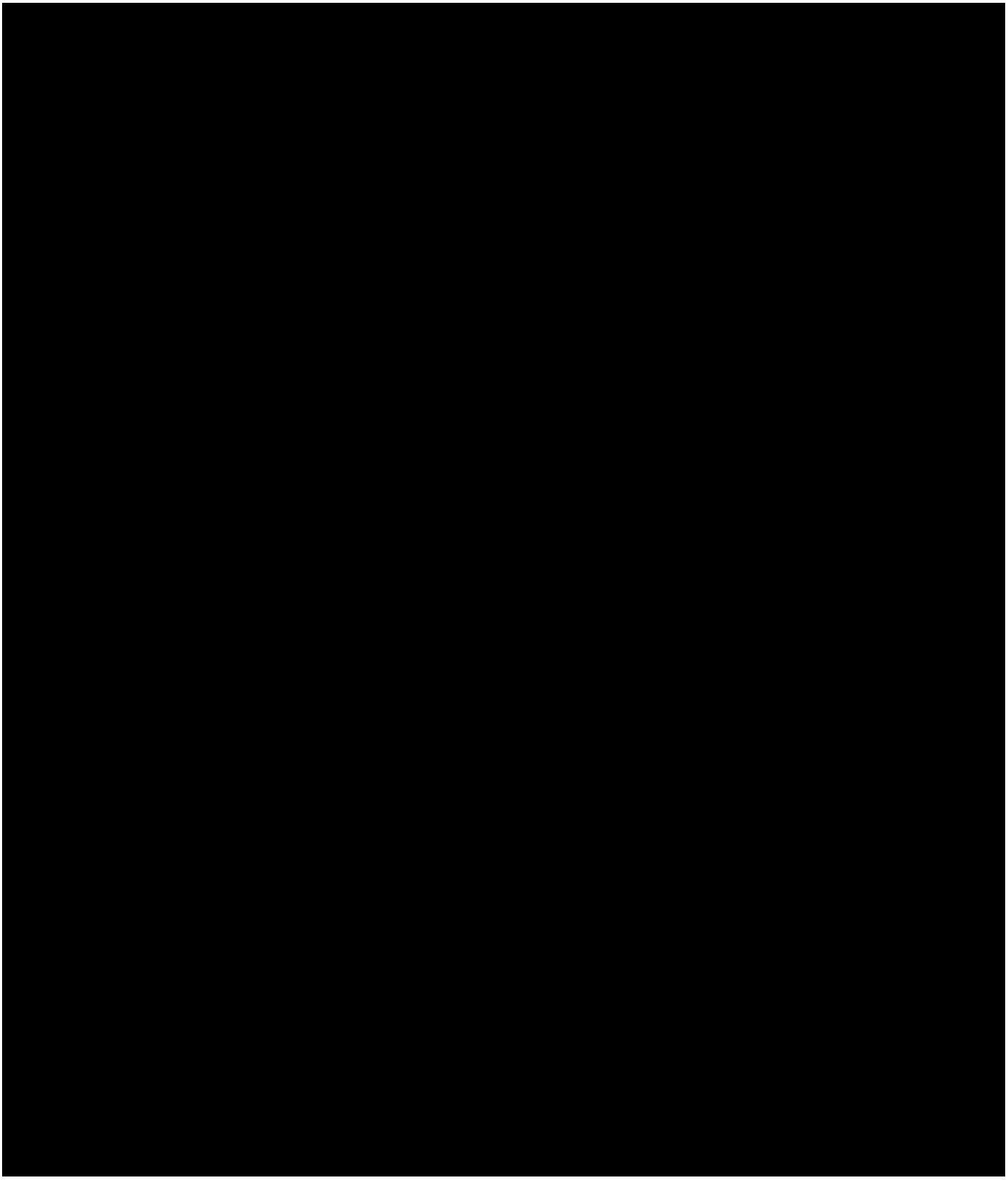
Safety data for the intervention and comparator in accordance with section 4.2 of the guideline is provided in Section 7.1.2.

Appendix F Comparative analysis of efficacy and safety

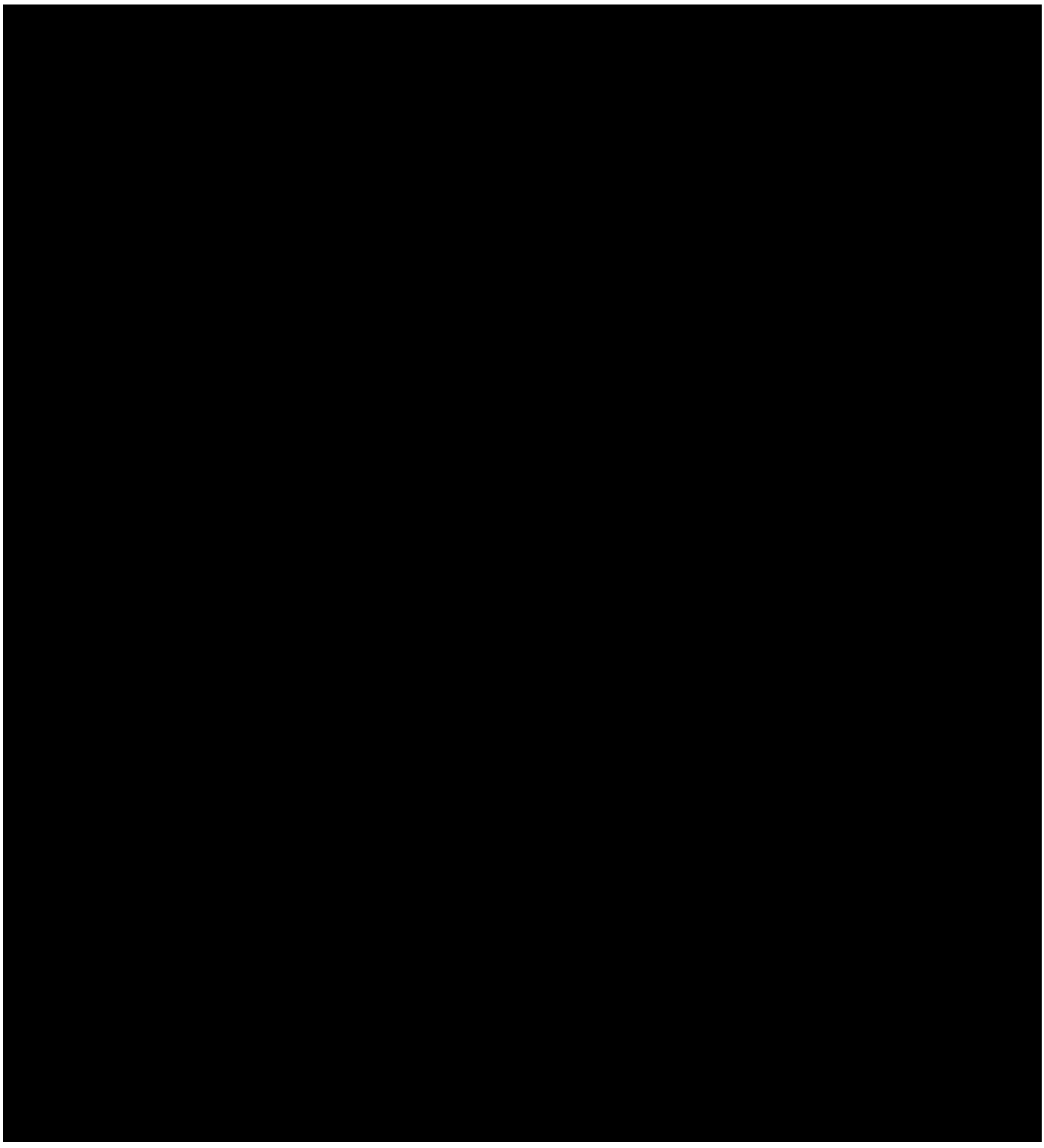
The IMpower010 study provides a direct comparison between atezolizumab and BSC and results can be used to address the clinical question. The comparative results for atezolizumab vs. BSC are presented in Section 7.1.2 and Appendix D.

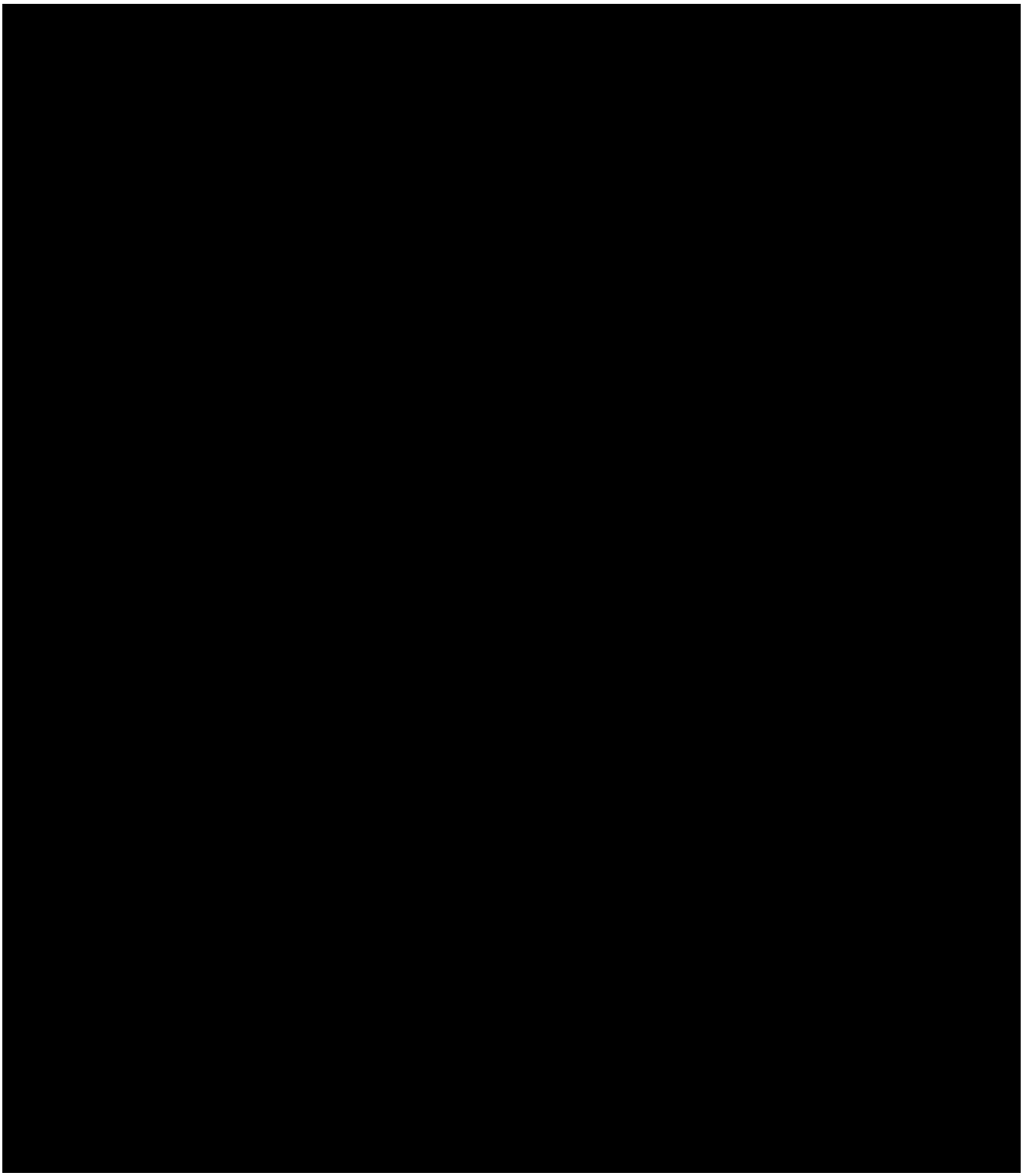
Appendix G Extrapolation

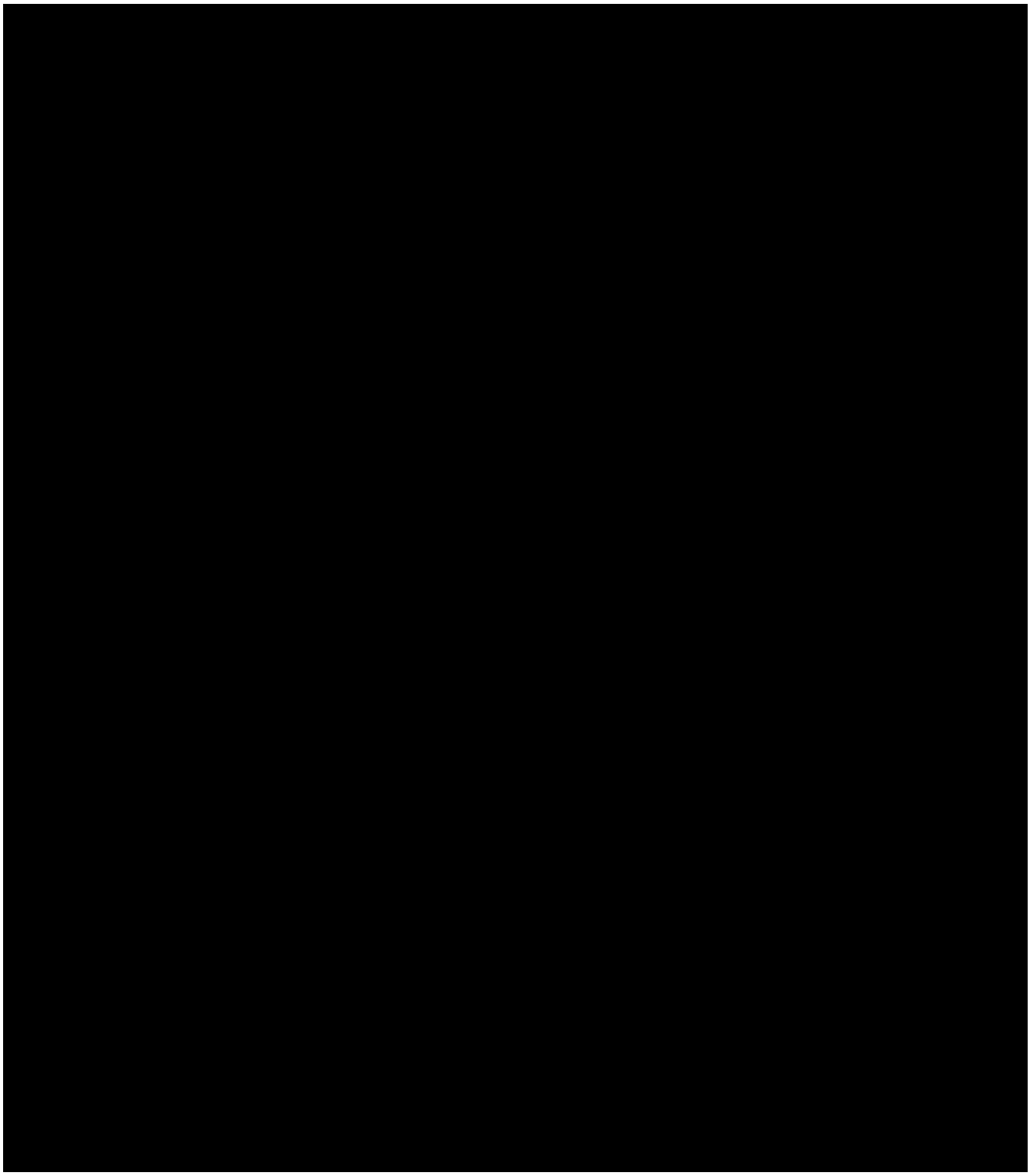


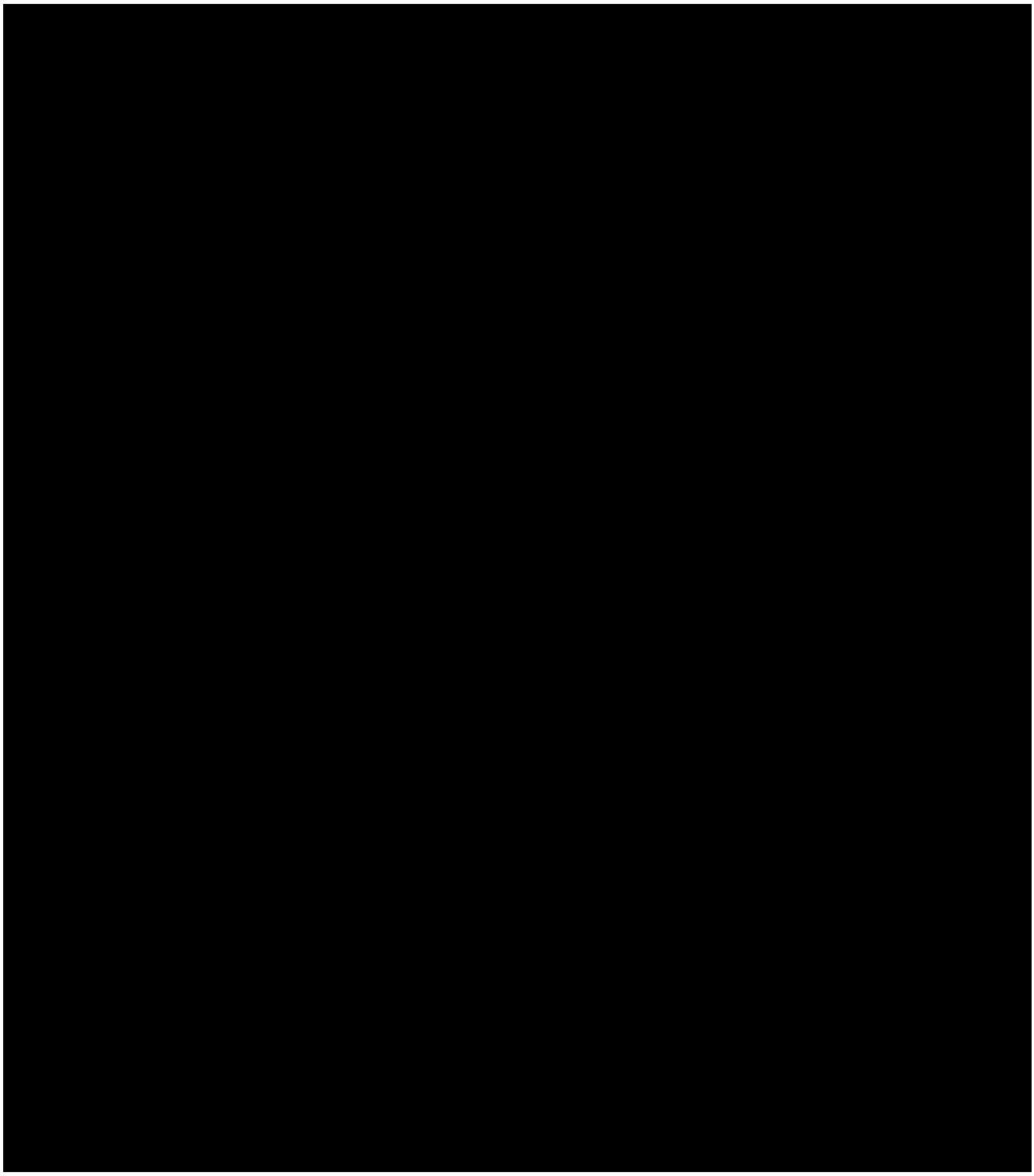


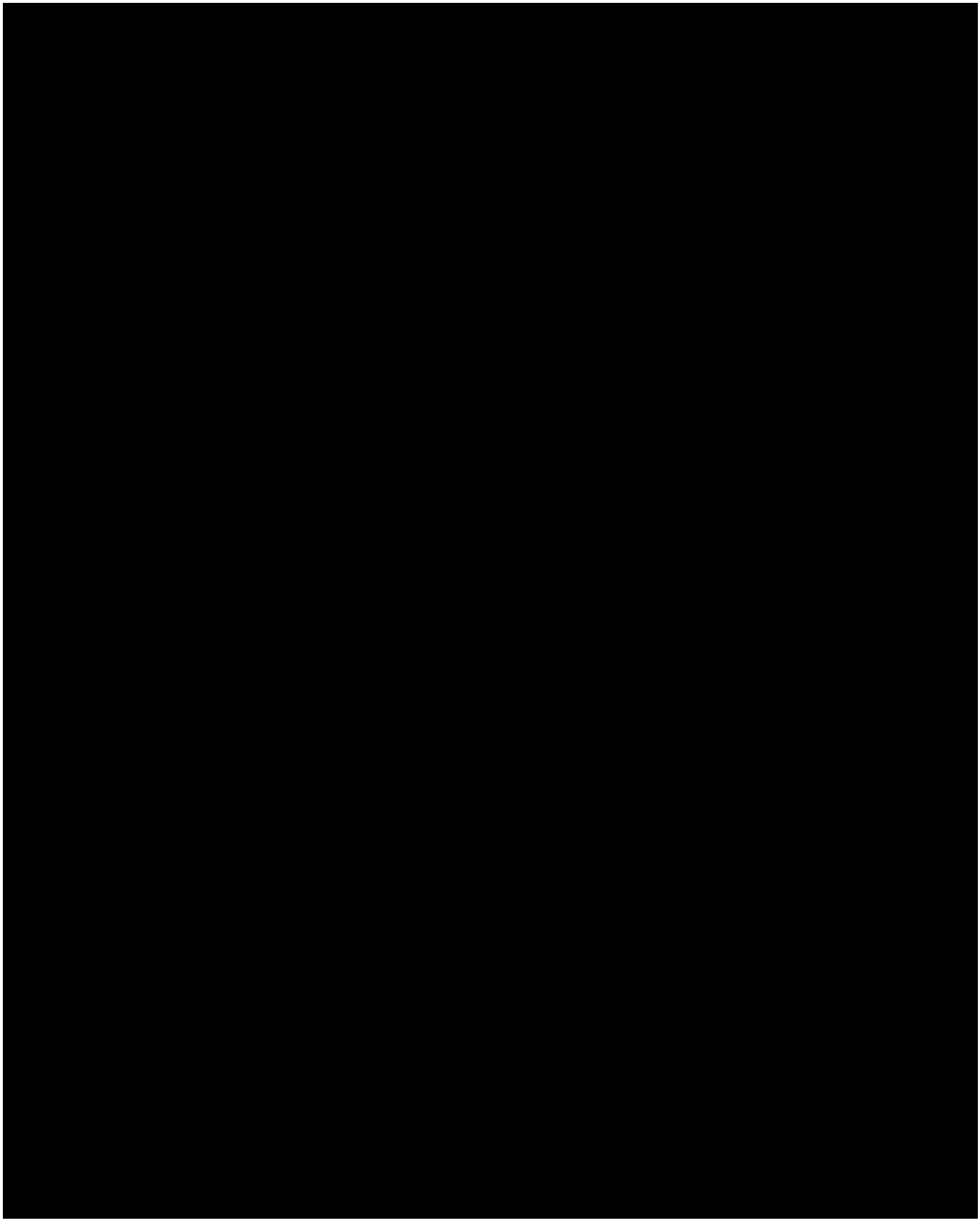
Smoothed hazard plots

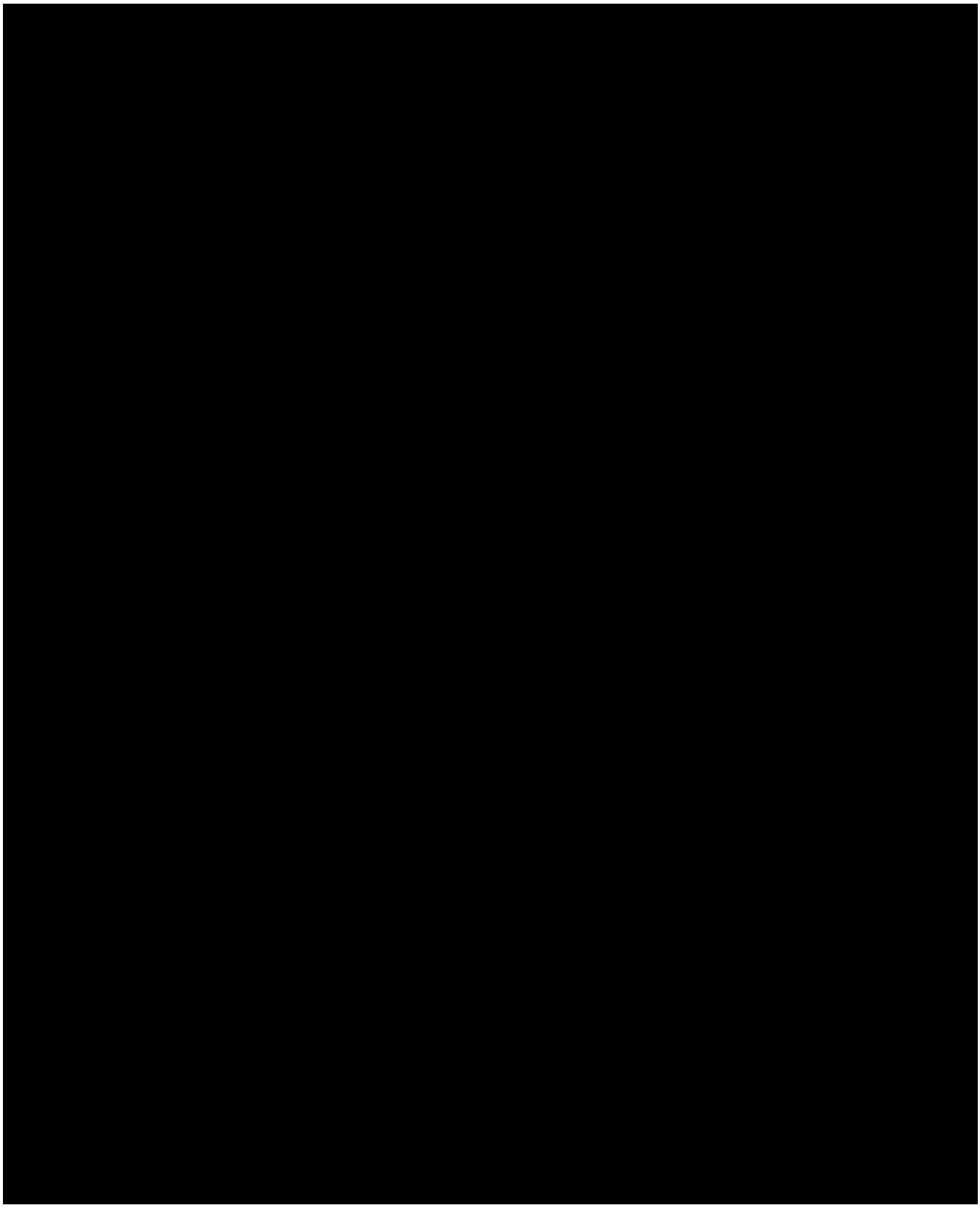


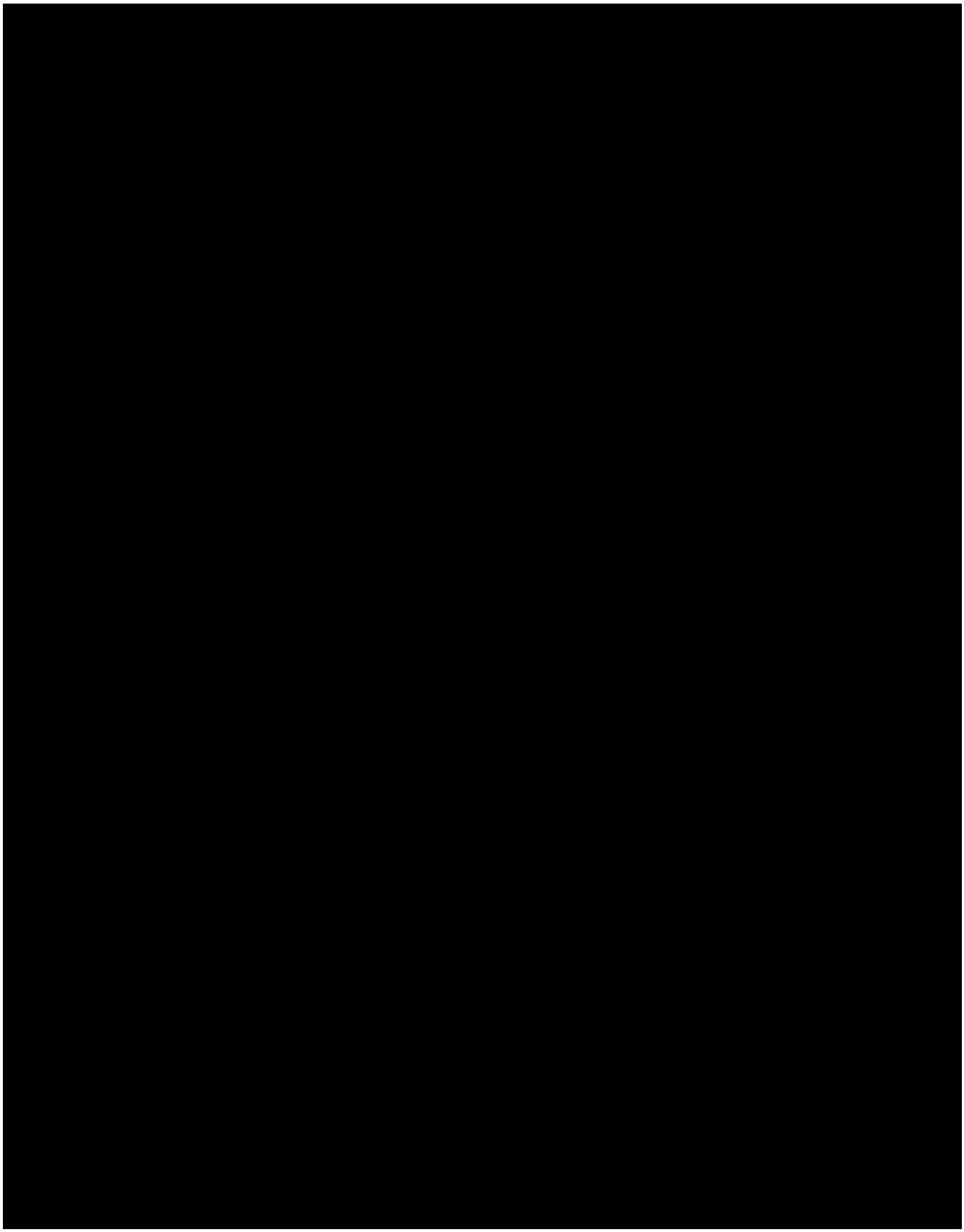


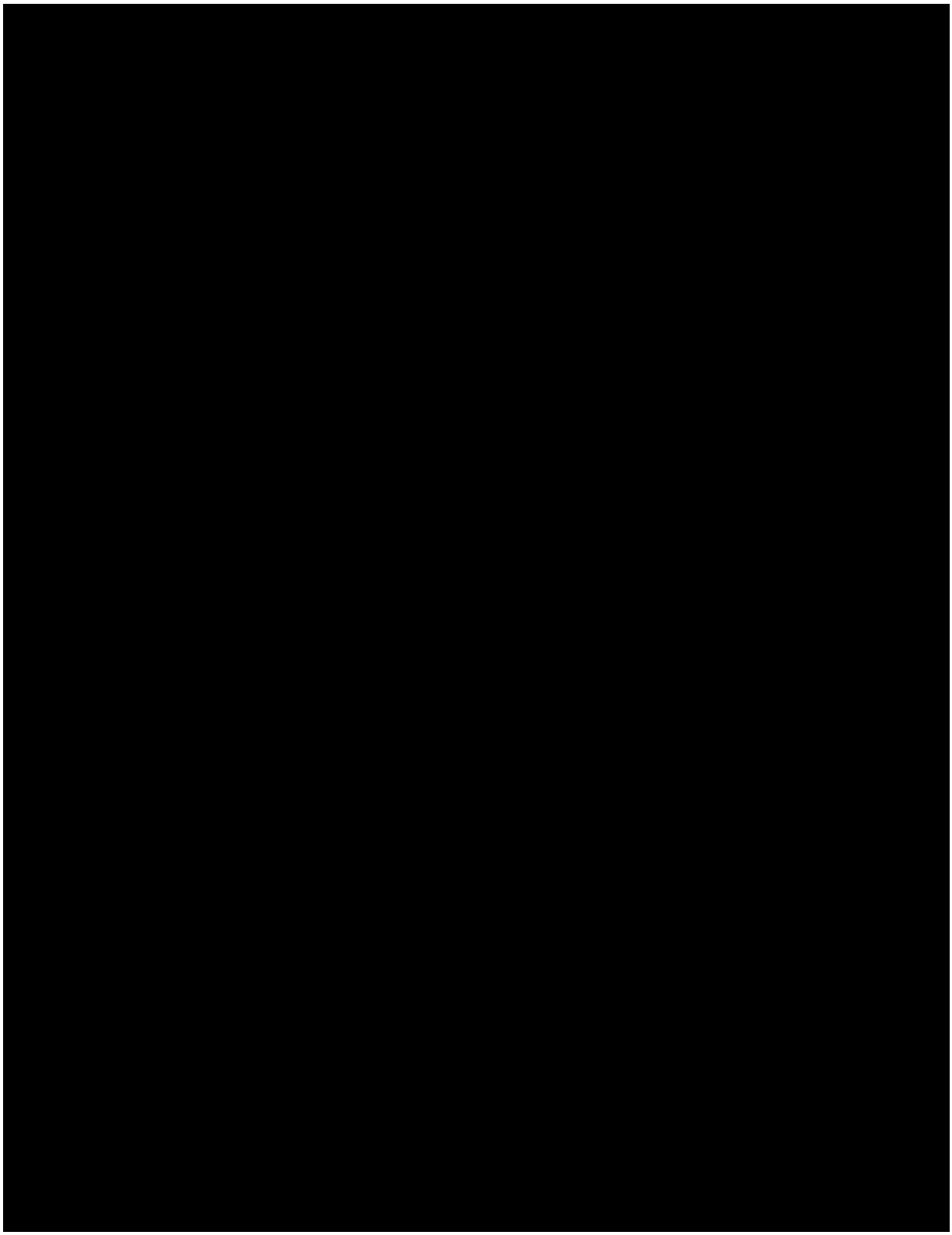












Appendix H Literature search for HRQoL data

A SLR was performed to identify studies that provide health related quality of life values for patients treating early NSCLC. The SLR is attached as a separate appendix, but a reduced description is provided below.

As part of the evidence generation strategy for atezolizumab in the adjuvant/neoadjuvant settings, a systematic literature review (SLR) was conducted to identify the following published evidence in early-stage NSCLC:

- Health state utility values (HSUVs) and health-related quality of life (HRQoL) data for relevant health states

The original review was conducted in March 2021 and was updated in June 2022. Table 48 presents the electronic databases searched via the Ovid platform on the 18th of March 2021 and the 22nd of June 2022, together with the sources hand searched to supplement the findings of the electronic databases.

Table 48: Bibliographic databases, conference websites, and HTA bodies included in the HRQoL literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	**Ovid**	**1974 to 2022**	**21.06.2022**
MEDLINE	**Ovid**	**1946 to 2022**	**21.06.2022**
*EMB Reviews incorporating:			
Cochrane Database of Systematic Reviews	**Ovid**	**2005 to 2022**	**15.06.2022**
American College of Physicians (ACP) Journal Club	**Ovid**	**1991 to 2022**	**May 2022**
Database of Abstracts of Reviews of Effects (DARE)	**Ovid**	**January 2016 to March 2016**	**May 2022**
Cochrane Clinical Answers	**Ovid**	**Unlimited – May 2022**	**22.06.2022**
Cochrane Central Register of Controlled Trials (CENTRAL)	**Ovid**	**Unlimited – May 2022**	**22.06.2022**

Database	Platform	Relevant period for the search	Date of search completion
Cochrane Methodology Register	**Ovid**	**July 2012 to September 2012**	**22.06.2022**
HTA database	**Ovid**	**October 2016 to December 2016**	**22.06.2022**
National Health Service Economic Evaluation Database (NHS EED)	**Ovid**	**January 2016 to March 2016**	**22.06.2022**
Supplementary sources			
Conferences:			
American Society of Clinical Oncology (ASCO)	**www.asco.org**	**2019 to 2022**	**21.06.2022**
European Society for Medical Oncology (ESMO)	**www.esmo.org**	**2018 to 2021**	**23.06.2022**
European Lung Cancer Congress (ELCC)	**www.esmo.org**	**2019 to 2022**	**24.06.2022**
International Association for the Study of Lung Cancer (IASLC)/World Conference on Lung Cancer (WCLC)	**www.iaslc.org**	**2018 to 2020**	**22.06.2022**
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	**www.ispor.org**	**2018 to 2022**	**24.06.2022**
ISPOR Asia Pacific	**www.ispor.org**	**2018 to 2020**	**07.04.2021**
ISPOR European Meetings	**www.ispor.org**	**2018 to 2022**	**22.06.2022**
Health Technology Assessment	**www.htai.org**	**2018 to 2022**	**07.04.2022**

Database	Platform	Relevant period for the search	Date of search completion
International (HTAi)			
Society for Medical Decision Making (SMDM), North American	**www.smdm.org**	**2018 to 2021**	**07.06.2022**
SMDM, Biennial European Meetings	**www.smdm.com**	**2018 to 2022**	**20.06.2022**
Additional databases/websites:			
EUROQoL Website	**www.eurogol.org**	**Unlimited – 28.06.2022**	**28.06.2022**
University of Sheffield's ScHARRHUD database	**www.scharrhud.org**	**Unlimited – 28.06.2022**	**28.06.2022**
International Network of Agencies for Health Technology Assessment (INAHTA)	**www.database.inahta.org**	**Unlimited – 28.06.2022**	**28.06.2022**
National Institute for Health Research (NIHR)	**www.journalslibrary.nihr.ac.uk**	**Unlimited – 29.06.2022**	**29.06.2022**
RePEc website (EconPapers)	**www.econpapers.repec.org**	**Unlimited – 05.07.2022**	**05.07.22**

Abbreviations: ACP - American College of Physicians, ASCO - American Society of Clinical Oncology, CENTRAL - Cochrane Central Register of Controlled Trials, DARE - Database of Abstracts of Reviews of Effects, ELCC - European Lung Cancer Congress, ESMO - European Society for Medical Oncology, HTA - Health Technology Assessment, HTAi - Health Technology Assessment International, IASLC - International Association for the Study of Lung Cancer, INAHTA - International Network of Agencies for Health Technology Assessment, ISPOR - International Society for Pharmacoeconomics and Outcomes Research, NHS EED - National Health Service Economic Evaluation Database, NIHR - National Institute for Health Research, SMDM - Society for Medical Decision Making, WCLC - World Conference on Lung Cancer

1.1 Search strategy

The eligibility criteria applied throughout the HSUV/HRQOL SLR are summarized in Table 49.

Table 49: Eligibility criteria

Criteria	Include	Exclude
POPULATION	Patients with early-stage NSCLC (resectable; stage 0/I/II/III) receiving treatment in the adjuvant or neoadjuvant treatment settings –	• Advanced/metastatic (stage IV) NSCLC

	no restriction with regard to patient age or mutation status *Note: the primary population of interest was patients with stage II-III resectable disease; however, studies considering patients with stage I-III disease were considered eligible during the screening process to assess the extent of evidence available.*	• Mixed populations where a breakdown of data for early-stage NSCLC is not provided
INTERVENTION & COMPARATORS	No restriction	-
OUTCOMES	• HSUVs (and disutilities [e.g. associated with progression or AEs]) for relevant health states (individual [patient or caregiver]) derived using the following techniques: ○ Generic, preference-based instruments (e.g. EQ-5D, SF-6D) ○ Direct methods (e.g. TTO, SG, VAS) ○ Mapping algorithms allowing data from disease-specific/generic measures to be mapped to preference-based HSUVs • Disease-specific/generic (non-utility) HRQOL data (e.g. EORTC-QLQ-C30) (studies tagged and provided as a list)	Outcomes not listed in "include" column
STUDY DESIGN	• Studies reporting original HSUV/HRQOL data	• Reviews/editorials† • Case reports • Pharmacokinetic studies • Animal/*in vitro* studies
GEOGRAPHY	No restriction: however, i8 countries (UK, France, Spain, Canada, Australia, Brazil, Germany and Italy), China, South Korea, Japan, and the US were primary territories of interest	-
PUBLICATION DATE	No restriction	-
LANGUAGE	No restriction: English language publications or non-English language publications with an English abstract were of primary interest.	-

Abbreviations: AE - adverse event, EORTC-QLQ-C30 - European Organization for Research and Treatment of Cancer Quality of Life questionnaire, EQ-5D - European Quality of Life-5 Dimensions, HRQOL - health-related quality of life, HSUV - health state utility value, NSCLC - non-small cell lung cancer, SF-6D - Short Form-6 Dimensions, SG - standard gamble, TTO - time trade off, UK - United Kingdom, US - United States, VAS - visual analogue scale.

†The reference lists of any relevant review publications were checked to ensure any relevant primary studies were considered for inclusion.

1.2 Systematic selection of studies

Original Review (March 2021)

Electronic searches of the following databases were conducted on the 18th of March 2021 via the Ovid platform: Embase, MEDLINE (including Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, and Daily), and EBM Reviews (incorporating: the Cochrane Database of Systematic Reviews; the ACP Journal Club; DARE; Cochrane Clinical Answers; Cochrane Central Register of Controlled Trials; the Cochrane Methodology Register; the HTA database; and NHS EED), for search algorithm, see Table 50 and Table 52. The electronic database searches were supplemented by hand searching of reference lists of included studies, relevant conference proceedings (last 3 years availability), and additional grey literature sources.

The electronic databases identified a total of 1,987 citations. Following the removal of 264 duplicates, 1,723 citations were screened on the basis of title and abstract. A total of 95 citations were considered to be potentially relevant and were obtained full-text review and 105 studies reporting use of generic/disease-specific HRQOL (non-utility) instruments were isolated and tagged. At the full publication review stage, a further 52 citations were excluded and an additional 28 HRQOL studies were tagged. Hand searching yielded 22 additional relevant publications (included HSUV studies, N=12; tagged HRQOL studies, N=10). This resulted in a total of 27 publications reporting HSUVs for patients with early stage NSCLC for final inclusion in the review (full publications, N=25; conference abstracts, N=2). In addition, 143 studies reporting generic and/or disease-specific HRQOL data were tagged.

June 2022 update

Electronic searches of the following databases were conducted on the 22nd of June 2022 via the Ovid platform: Embase, MEDLINE (including Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, and Daily), and EBM Reviews (incorporating: the Cochrane Database of Systematic Reviews; the ACP Journal Club; DARE; Cochrane Clinical Answers; Cochrane Central Register of Controlled Trials; the Cochrane Methodology Register; the HTA database; and NHS EED), for search algorithm, see Table 53, Table 54, and Table 55. The electronic database searches were supplemented by hand searching of reference lists of included studies, relevant conference proceedings (conducted after the original search to June 2022), and additional grey literature sources.

The electronic database search identified 293 citations. After the removal of 91 duplicates from the current search and 15 duplicates of the original search (March 2021), 187 citations were screened on the basis of title and abstract. A total of seven publications were deemed potentially relevant and were obtained for full-text review and 12 publications reporting the use of generic/disease-specific HRQOL (non-utility) instruments were isolated and tagged. At the full publication review stage, a further three publications were excluded and two additional HRQOL studies were tagged. Hand searching yielded two additional HRQOL-tagged studies. This resulted in two new HSUV publications for patients with early-stage NSCLC being identified for final inclusion in the review update. A total of 16 studies reporting generic and/or disease-specific HRQOL data were tagged.

Search algorithm

Original review (March 2021)

Embase 1974 to 2021 March 17
Accessed 18th March 2021

Table 50. Embase, Original review March 2021

	Searches	Results
1	exp lung non small cell cancer/ or exp non small cell lung cancer/	107597
2	((lung* or pulmonary) adj2 (carcinom* neoplasm* or cancer* or tumo?r* or malignan*)).mp.	378624
3	non.mp.	3480438
4	2 and 3	164867
5	NSCLC.mp.	88384
6	1 or 4 or 5	200123
7	(resectable or resected).mp.	129642
8	(early or early-stage or early stage).mp.	2216301
9	("stage 0" or "stage 1" or "stage I" or "stage 2" or "stage II" or "stage 3*" or "stage III*").mp.	205002
10	or/7-9	2487366
11	6 and 10	47446
12	quality adjusted life year/	28558
13	(quality adjusted or adjusted life year$).ti,ab,kw.	27059
14	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kw.	21974
15	(illness state$1 or health state$1).ti,ab,kw.	12141
16	(hui or hui1 or hui2 or hui3).ti,ab,kw.	2496
17	(multiattribute$ or multi attribute$).ti,ab,kw.	1259
18	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw.	26215
19	utilities.ti,ab,kw.	12618
20	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw.	23672
21	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw.	6946
22	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw.	40185
23	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	2959
24	"quality of life"/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw.	27290
25	"quality of life"/ and ec.fs.	45387

26	"quality of life"/ and (health adj3 status).ti,ab,kw.	17312
27	(quality of life or qol).ti,ab,kw. and "cost benefit analysis"/	5797
28	((qol or hrqol or quality of life).ti,kw. or "quality of life"/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab.	141678
29	"cost benefit analysis"/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kw.	892
30	"quality of life"/ and (quality of life or qol).ti.	106699
31	"quality of life"/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kw.	81779
32	"quality of life"/ and health-related quality of life.ti,ab,kw.	63036
33	economic model/	2364
34	or/12-33	360063
35	11 and 34	1205

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) 1946 to March 17, 2021

Accessed 18th March 2021

Table 51. Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) , Original review March 2021

	Searches	Results
1	exp Carcinoma, Non-Small-Cell Lung/	56016
2	((lung* or pulmonary) adj2 (carcinom* neoplasm* or cancer* or tumo?r* or malignan*)).mp.	190753
3	non.mp.	9608687
4	2 and 3	114637
5	NSCLC.mp.	47108
6	1 or 4 or 5	123598
7	(resectable or resected).mp.	84623
8	(early or early-stage or early stage).mp.	1633295
9	("stage 0" or "stage 1" or "stage I" or "stage 2" or "stage II" or "stage 3*" or "stage III*").mp.	114935
10	or/7-9	1797938
11	6 and 10	25731
12	Quality-Adjusted Life Years/	13009
13	(quality adjusted or adjusted life year$).ti,ab,kf.	18281
14	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kf.	11611
15	(illness state$1 or health state$1).ti,ab,kf.	6920

16	(hui or hui1 or hui2 or hui3).ti,ab,kf.	1628
17	(multiattribute$ or multi attribute$).ti,ab,kf.	978
18	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf.	16321
19	utilities.ti,ab,kf.	7639
20	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf.	12820
21	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf.	4517
22	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.	23153
23	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.	1998
24	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf.	12297
25	quality of life/ and ec.fs.	10470
26	quality of life/ and (health adj3 status).ti,ab,kf.	9476
27	(quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/	13528
28	((qol or hrqol or quality of life).ti,kw. or "quality of life"/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab.	60902
29	Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf.	3826
30	quality of life/ and (quality of life or qol).ti.	61538
31	quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf.	29449
32	quality of life/ and health-related quality of life.ti,ab,kf.	34206
33	Models, Economic/	10481
34	or/12-33	183855
35	11 and 34	432

EBM Reviews - Cochrane Database of Systematic Reviews 2005 to March 3, 2021, **EBM Reviews - ACP Journal Club** 1991 to February 2021, **EBM Reviews - Database of Abstracts of Reviews of Effects** 1st Quarter 2016, **EBM Reviews - Cochrane Clinical Answers** February 2021, **EBM Reviews - Cochrane Central Register of Controlled Trials** February 2021, **EBM Reviews - Cochrane Methodology Register** 3rd Quarter 2012, **EBM Reviews - Health Technology Assessment** 4th Quarter 2016, **EBM Reviews - NHS Economic Evaluation Database** 1st Quarter 2016
Accessed 18th March 2021

Table 52. EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - ACP Journal Club, EBM Reviews - Database of Abstracts of Reviews of Effects, EBM Reviews - Cochrane Clinical Answers, EBM Reviews - Cochrane Central Register of Controlled Trials, EBM Reviews - Cochrane Methodology Register,

EBM Reviews - Health Technology Assessment, EBM Reviews - NHS Economic Evaluation Database, Original review March 2021

	Searches	Results
1	exp Carcinoma, Non-Small-Cell Lung/	4694
2	((lung* or pulmonary) adj2 (carcinom* neoplasm* or cancer* or tumo?r* or malignan*)).mp.	24499
3	non.mp.	266659
4	2 and 3	16349
5	NSCLC.mp.	10335
6	1 or 4 or 5	17277
7	(resectable or resected).mp.	8864
8	(early or early-stage or early stage).mp.	140794
9	("stage 0" or "stage 1" or "stage I" or "stage 2" or "stage II" or "stage 3*" or "stage III*").mp.	28713
10	or/7-9	171216
11	6 and 10	6258
12	Quality-Adjusted Life Years/	4561
13	(quality adjusted or adjusted life year$).ti,ab,kf.	5171
14	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kf.	4152
15	(illness state$1 or health state$1).ti,ab,kf.	1343
16	(hui or hui1 or hui2 or hui3).ti,ab,kf.	285
17	(multiattribute$ or multi attribute$).ti,ab,kf.	85
18	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf.	5285
19	utilities.ti,ab,kf.	1268
20	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf.	10204
21	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf.	3374
22	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.	12265
23	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.	315
24	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf.	2825
25	quality of life/ and ec.fs.	2807
26	quality of life/ and (health adj3 status).ti,ab,kf.	1074
27	(quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/	1839

28	((qol or hrqol or quality of life).ti,kw. or "quality of life"/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab.	24995
29	Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf.	547
30	quality of life/ and (quality of life or qol).ti.	6187
31	quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf.	7258
32	quality of life/ and health-related quality of life.ti,ab,kf.	4601
33	Models, Economic/	1570
34	or/12-33	59564
35	11 and 34	350

June 2022 update

Embase 1974 to 2022 June 21
Accessed 22nd June 2022

Table 53. Embase, June 2022 update

#	Searches	Results
1	exp lung non small cell cancer/ or exp non small cell lung cancer/	129663
2	((lung* or pulmonary) adj2 (carcinom* neoplasm* or cancer* or tumo?r* or malignan*)).mp.	416007
3	non.mp.	3819008
4	2 and 3	186087
5	NSCLC.mp.	99761
6	1 or 4 or 5	226112
7	(resectable or resected).mp.	138389
8	(early or early-stage or early stage).mp.	2391936
9	("stage 0" or "stage 1" or "stage I" or "stage 2" or "stage II" or "stage 3*" or "stage III*").mp.	223608
10	or/7-9	2684573
11	6 and 10	52678
12	quality adjusted life year/	31625
13	(quality adjusted or adjusted life year$).ti,ab,kw.	30006
14	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kw.	24323
15	(illness state$1 or health state$1).ti,ab,kw.	13233
16	(hui or hui1 or hui2 or hui3).ti,ab,kw.	2780
17	(multiattribute$ or multi attribute$).ti,ab,kw.	1366
18	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw.	28369

19	utilities.ti,ab,kw.	13697
20	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw.	27071
21	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw.	7857
22	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw.	42825
23	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	3204
24	"quality of life"/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw.	29973
25	"quality of life"/ and ec.fs.	52536
26	"quality of life"/ and (health adj3 status).ti,ab,kw.	18295
27	(quality of life or qol).ti,ab,kw. and "cost benefit analysis"/	6386
28	((qol or hrqol or quality of life).ti,kw. or "quality of life"/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab.	157953
29	"cost benefit analysis"/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kw.	1074
30	"quality of life"/ and (quality of life or qol).ti.	116810
31	"quality of life"/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kw.	90984
32	"quality of life"/ and health-related quality of life.ti,ab,kw.	70173
33	economic model/	2783
34	or/12-33	399439
35	11 and 34	1369
36	limit 35 to yr="2021 -Current"	167

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) 1946 to June 21, 2022

Accessed 22nd June 2022

Table 54. MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R), June 2022 update

#	Searches	Results
1	exp Carcinoma, Non-Small-Cell Lung/	65144
2	((lung* or pulmonary) adj2 (carcinom* neoplasm* or cancer* or tumo?r* or malignan*)).mp.	211324
3	non.mp.	10252263
4	2 and 3	128253
5	NSCLC.mp.	54565
6	1 or 4 or 5	138124
7	(resectable or resected).mp.	90828
8	(early or early-stage or early stage).mp.	1774516

9	("stage 0" or "stage 1" or "stage I" or "stage 2" or "stage II" or "stage 3*" or "stage III*").mp.	124969
10	or/7-9	1952208
11	6 and 10	28684
12	Quality-Adjusted Life Years/	14886
13	(quality adjusted or adjusted life year$).ti,ab,kf.	21023
14	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kf.	13287
15	(illness state$1 or health state$1).ti,ab,kf.	7710
16	(hui or hui1 or hui2 or hui3).ti,ab,kf.	1813
17	(multiattribute$ or multi attribute$).ti,ab,kf.	1140
18	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf.	18397
19	utilities.ti,ab,kf.	8581
20	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf.	15186
21	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf.	5291
22	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.	25066
23	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.	2193
24	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf.	14361
25	quality of life/ and ec.fs.	10869
26	quality of life/ and (health adj3 status).ti,ab,kf.	10947
27	(quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/	15812
28	((qol or hrqol or quality of life).ti,kw. or "quality of life"/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab.	74064
29	Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf.	4741
30	quality of life/ and (quality of life or qol).ti.	70457
31	quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf.	36646
32	quality of life/ and health-related quality of life.ti,ab,kf.	40807
33	Models, Economic/	11006
34	or/12-33	212711
35	11 and 34	521
36	limit 35 to yr="2021 -Current"	83

EBM Reviews - Cochrane Database of Systematic Reviews 2005 to June 15, 2022, **EBM Reviews - ACP Journal Club** 1991 to May 2022, **EBM Reviews - Database of Abstracts of Reviews of Effects** 1st Quarter 2016, **EBM Reviews - Cochrane Clinical Answers** May 2022, **EBM Reviews - Cochrane Central Register of Controlled Trials** May 2022, **EBM Reviews - Cochrane Methodology**

Register 3rd Quarter 2012, **EBM Reviews - Health Technology Assessment** 4th Quarter 2016, **EBM Reviews - NHS Economic Evaluation Database** 1st Quarter 2016
Accessed 22nd June 2022

Table 55. EBM Reviews, June 2022 Update

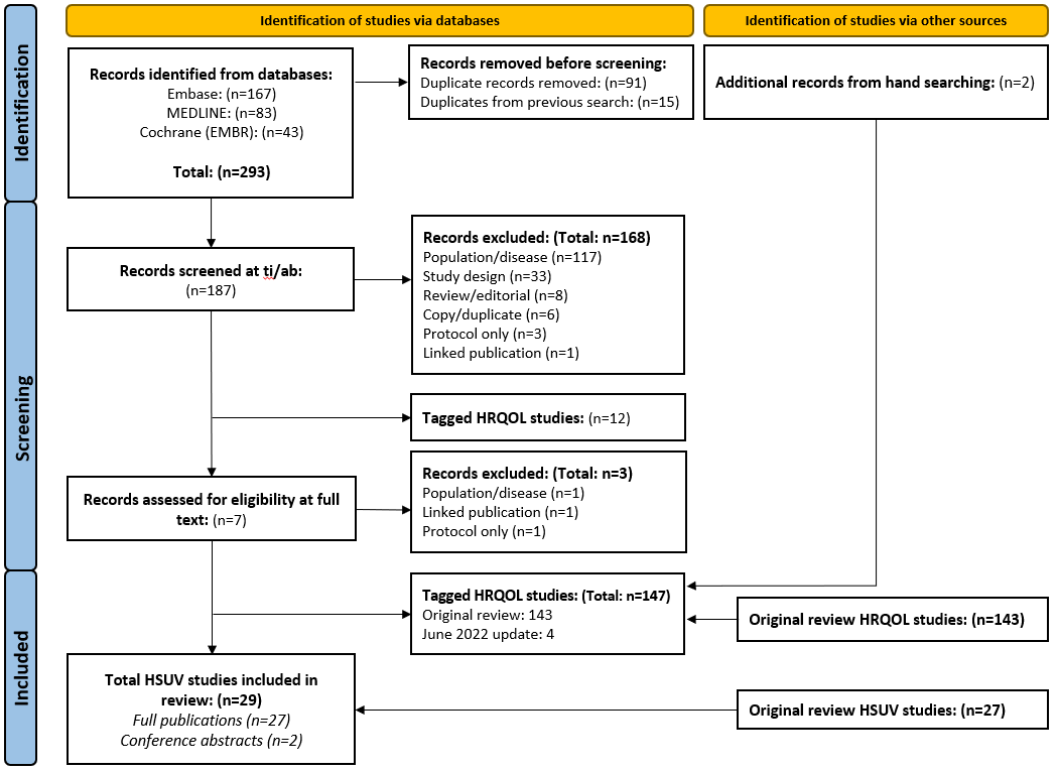
#	Searches	Results
1	exp Carcinoma, Non-Small-Cell Lung/	4825
2	((lung* or pulmonary) adj2 (carcinom* neoplasm* or cancer* or tumo?r* or malignan*)).mp.	24468
3	non.mp.	273574
4	2 and 3	16541
5	NSCLC.mp.	10970
6	1 or 4 or 5	17491
7	(resectable or resected).mp.	9255
8	(early or early-stage or early stage).mp.	145751
9	("stage 0" or "stage 1" or "stage I" or "stage 2" or "stage II" or "stage 3*" or "stage III*").mp.	29899
10	or/7-9	177377
11	6 and 10	6429
12	Quality-Adjusted Life Years/	1481
13	(quality adjusted or adjusted life year$).ti,ab,kf.	5695
14	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kf.	4579
15	(illness state$1 or health state$1).ti,ab,kf.	1422
16	(hui or hui1 or hui2 or hui3).ti,ab,kf.	288
17	(multiattribute$ or multi attribute$).ti,ab,kf.	85
18	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf.	4372
19	utilities.ti,ab,kf.	1327
20	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf.	11545
21	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf.	3390
22	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.	13100
23	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.	307
24	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf.	2625
25	quality of life/ and ec.fs.	1696
26	quality of life/ and (health adj3 status).ti,ab,kf.	1204
27	(quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/	2980
28	((qol or hrqol or quality of life).ti,kw. or "quality of life"/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab.	23281

29	Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf.	660
30	quality of life/ and (quality of life or qol).ti.	6852
31	quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf.	6596
32	quality of life/ and health-related quality of life.ti,ab,kf.	5319
33	Models, Economic/	264
34	or/12-33	56350
35	11 and 34	332
36	limit 35 to yr="2021 -Current"	43

Overall summary

Across the original review (March 2021) and the June 2022 update, a total of 29 relevant HSUV studies were identified for inclusion (full publications, n=27; conference abstracts, n=2). The overall flow of studies through the review is summarized in the PRISMA flow diagram in Figure 32

Figure 32. PRISMA flow diagram for HSUV SLR



Abbreviations: HSUV – health state utility value, HRQOL – health-related quality of life, SLR – systematic literature review, ti/a – title and abstract

1.3 Description of identified studies: full publications

Summary of reported HSUVs

Of the 29 eligible studies identified by the original SLR and the two identified in the June 2022 update, a total of 27 were presented as full publications [1-27]. Countries from which the utility data were derived included: the US (N=6) [2, 3, 5, 20, 21, 23]; Canada (N=3) [10, 11, 17]; Denmark (N=3) [4, 7, 12];

Netherlands (N=3) [8, 24, 25]; Finland (N=2) [9, 18]; Taiwan (N=2) [26, 27]; the UK (N=2) [13, 19]; Australia (N=1) [16]; Italy (N=1) [22]; Japan (N=1) [15]; and South Korea (N=1) [14]. Two studies were multi-national; one study considered France, Germany, and the UK [1], and one was a review reporting pooled utility estimates [6].

The following patient populations were considered across the 27 studies:

- Patients with stage I-IV NSCLC (N=11) [5, 6, 8, 10, 13, 16, 20-22, 26, 27];
- Patients with resected stage I-III/localised NSCLC (N=4) [1, 9, 15, 18];
- Patients with stage I NSCLC (N=3) [2, 4, 25];
- Adult patients with completely resected early-stage (T2N0, T1N1, or T2N1) NSCLC receiving adjuvant therapy (N=1) [11];
- Patients with a diagnosis of T1-2N0M0 (localised) NSCLC treated with SBRT (N=1) [12];
- Patients with stage I-III lung cancer (N=1) [3];
- Patients at high risk for development of post-operative pulmonary complications following lung resection due to lung cancer or diagnostic lung resections (N=1) [7];
- Adult ambulatory cancer survivors, including lung cancer (N=1) [17];
- Patients with known/suspected NSCLC with no evidence of distant metastatic disease (N=1) [19];
- Patients with stage I-III NSCLC receiving definitive chemoradiation (N=1) [23];
- Patients with stage III NSCLC (N=1) [24];
- Adult members from the Korean general population (proxy respondents) (N=1) [14].

Sixteen studies reported intervention-specific utilities; the treatments considered included:

- Surgery, chemotherapy, and/or radiotherapy (N=3) [8, 10, 22];
- VATS vs thoracotomy (N=2) [4, 18];
- Surgery (not specified) (N=2) [7, 16];
- Lobectomy/bilobectomy (N=2) [2, 9];
- Vinorelbine + cisplatin vs observation (N=1) [11];
- Stereotactic body radiation therapy (SBRT) vs surgery (N=1) [25];
- SBRT + comprehensive geriatric assessment (CGA) vs SBRT alone (N=1) [12];
- Endobronchial ultrasound (EBUS)/ endoscopic ultrasound (EUS) vs surgical staging (N=1) [19];
- Prophylactic cranial irradiation vs observation (N=1) [24];
- VATS (N=1) [15];
- Chemoradiation (N=1) [23].

Utilities were also reported for the following patient-related and disease-related health states:

- Disease stage (N=10) [2, 5, 6, 8, 10, 14, 20, 21, 26, 27];
- Disease free, locoregional recurrence, and/or distant metastasis (N=4) [1, 8, 17, 22];
- Time since diagnosis (N=2) [5, 22];
- Resectability status (N=2) [16, 27];
- AEs (N=1) [8].

A summary of the 27 full publications is provided in Table 56. Color coding has been used to indicate the following: GREEN: health states relevant to patients with stage II/III(A) disease; ORANGE: uncertainty in the method used to derive utilities (instrument and/or social tariff unclear); RED: intervention-specific health state where surgery +/- adjuvant chemotherapy is not used (e.g., relates to radiotherapy use); BLUE: both GREEN and RED criteria apply.

Table 56. Summary of published HSUV data associated with patients with early NSCLC (N=27)

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
Original review (N=25)					
Andreas, 2018 [1] Multi-national (France, Germany, and UK)	Patients with completely resected stage IB-IIIA NSCLC (N=306)	**Instrument:** EQ-5D (version not specified) **Tariff:** NR	Patients with resected stage IB-IIIA NSCLC, disease free (N=238)	0.72 [0.68, 0.75]	**Conclusions:** HRQOL measures suggested a higher utility score during the period of distant metastasis and/or terminal disease than in the period of locoregional recurrence. **Limitations:** • Limited sample size may be a source of imprecision. • Study data not guaranteed to be representative of all sites and physicians treating patients with stage IB-IIIA NSCLC across each country. • External validation of medical record data not possible.
			Patients with resected stage IB-IIIA NSCLC, locoregional recurrence (N=19)	0.62 [0.51, 0.74]	
			Patients with resected stage IB-IIIA NSCLC, distant metastasis/terminal disease (N=32)	0.67 [0.55, 0.78]	
Bendixen, 2019 [4] Denmark	Patients with stage I NSCLC (N=206)	**Instrument:** EQ-5D-3L **Tariff:** Danish tariff	Patients with stage I NSCLC, baseline (pre-operative), VATS (N=63)	0.89 (0.13)	**Conclusions:** VATS is a cost-effective alternative to thoracotomy following lobectomy for stage I lung cancer. **Limitations:** • None reported
			Patients with stage I NSCLC, baseline (pre-operative), thoracotomy (N=61)	0.86 (0.15)	
			Patients with stage I NSCLC, 2 weeks post-operatively, VATS (N=78)	0.78 (0.17)	
			Patients with stage I NSCLC, 2 weeks post-operatively, thoracotomy (N=80)	0.73 (0.14)	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
			Patients with stage I NSCLC, 4 weeks post-operatively, VATS (N=78)	0.82 (0.17)	
			Patients with stage I NSCLC, 4 weeks post-operatively, thoracotomy (N=73)	0.75 (0.18)	
			Patients with stage I NSCLC, 8 weeks post-operatively, VATS (N=81)	0.85 (0.16)	
			Patients with stage I NSCLC, 8 weeks post-operatively, thoracotomy (N=71)	0.81 (0.13)	
			Patients with stage I NSCLC, 12 weeks post-operatively, VATS (N=83)	0.87 (0.14)	
			Patients with stage I NSCLC, 12 weeks post-operatively, thoracotomy (N=71)	0.85 (0.14)	
			Patients with stage I NSCLC, 26 weeks post-operatively, VATS (N=81)	0.86 (0.18)	
			Patients with stage I NSCLC, 26 weeks post-operatively, thoracotomy (N=73)	0.85 (0.14)	
			Patients with stage I NSCLC, 52 weeks post-operatively, VATS (N=74)	0.86 (0.16)	
			Patients with stage I NSCLC, 52 weeks post-operatively, thoracotomy (N=66)	0.84 (0.18)	
Black, 2014 [5] US	Patients with stage I-IV NSCLC (sample size NR)	**Instrument:** SF-6D **Tariff:** NR	Patients with stage IA NSCLC, <12 months since diagnosis	0.696	**Conclusions:** no conclusions reported relating to HRQOL **Limitations:** • Factors relating to generalisability of results beyond the study setting were not considered.
			Patients with stage IA NSCLC, 12+ months since diagnosis	0.718	
			Patients with stage IB NSCLC, <12 months since diagnosis	0.727	
			Patients with stage IB NSCLC, 12+ months since diagnosis	0.711	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
			Patients with stage II NSCLC, <12 months since diagnosis	0.600	
			Patients with stage II NSCLC, 12+ months since diagnosis	0.684	
			Patients with stage III NSCLC, <12 months since diagnosis	0.614	
			Patients with stage III NSCLC, 12+ months since diagnosis	0.716	
			Patients with stage IV NSCLC, <12 months since diagnosis	0.612	
			Patients with stage IV NSCLC, 12+ months since diagnosis	0.623	
Blom, 2020 [6] Multi-national (review)	Patients with stage I-IV lung cancer (N=5,100†)	**Instrument:** multiple (pooled estimate) **Tariff:** multiple (pooled estimate)	Patients with lung cancer, all stages (N=5,100)	0.68 [0.61, 0.75]	**Conclusions:** the pooled HSUVs reported in this study may provide the best available stage-specific HSUVs for most countries. **Limitations:** • Heterogeneity across studies included in the analysis.
			Patients with lung cancer, stages I-II (N=1,510)	0.78 [0.70, 0.86]	
			Patients with lung cancer, stages III-IV (N=4,703)	0.69 [0.65, 0.73]	
Brocki, 2018 [7] Denmark	Patients at high risk for development of post-operative pulmonary complications following lung resection due to lung cancer or diagnostic lung resections (N=68)	**Instrument:** EQ-5D-5L **Tariff:** Danish tariff (assumed)	Patients with lung cancer who have undergone resection, males, baseline	0.855 (0.11)	**Conclusions:** post-operative inspiratory muscle training in addition to standard physiotherapy, including early mobilisation, may prevent a decline in physical activity level 2 weeks post-operatively in high-risk patients undergoing lung resection. **Limitations:**
			Patients with lung cancer who have undergone resection, females, baseline	0.803 (0.151)	
			Patients with lung cancer who have undergone resection, 2 weeks post-operatively, mean change from baseline	-0.127 [-0.168, -0.085]	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
			Patients with lung cancer who have undergone resection, 2 weeks post-operatively, mean change from baseline, difference between intervention and control group	-0.016 [-0.091, 0.060]	• Relatively small number of participants may limit the generalisability of results to the general population undergoing lung cancer surgery.
Grutters, 2010 [8] Netherlands	Patients treated for NSCLC between 2004 and 2007 (N=245)	**Instrument:** EQ-5D-3L **Tariff:** UK tariff (assumed from reference to Dolan et al [1997] [28])	Patients with NSCLC, initial tumour stage I (N=105)	0.77 (0.26)	**Conclusions:** results of the present study provide original data on HRQOL during survival of NSCLC; AEs were found to have a considerable impact on HRQOL. **Limitations:** • Some relatively small subgroups based on initial treatment modality. • AEs were self-reported by respondents rather than by the physician. • High proportion of patients treated with surgery indicates a relatively "healthy" sample.
			Patients with NSCLC, initial tumour stage II (N=39)	0.74 (0.22)	
			Patients with NSCLC, initial tumour stage III (N=99)	0.70 (0.29)	
			Patients with NSCLC, initial tumour stage IV (N=2)	0.86 (0.19)	
			Patients with stage I-IV NSCLC, recurrence (N=34)	0.61 (0.37)	
			Patients with stage I-IV NSCLC, no recurrence (N=177)	0.76 (0.24)	
			Patients with stage I-IV NSCLC, no severe AE (N=200)	0.80 (0.20)	
			Patients with stage I-IV NSCLC, serious AE (N=41)	0.45 (0.33)	
Ilonen, 2010 [9] Finland	Patients with stage IA-IIIB NSCLC who underwent surgery (lobectomy or bilobectomy) between May	**Instrument:** 15D **Tariff:** NR	Patients with stage IA-IIIB NSCLC undergoing lobectomy/bilobectomy, pre-operative (baseline) (N=53)	0.898	**Conclusions:** lobectomy and bilobectomy are associated with a significant negative long-term post-operative HRQOL in patients with NSCLC.

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
	2002 and November 2005 (N=53)		Patients with stage IA-IIIB NSCLC undergoing lobectomy/bilobectomy, change from baseline at 3 months post-operatively (N=48)	-0.069 (p=0.001)	**Limitations:** • HRQOL may be overestimated as it is generally noticed that those with advanced cancer do not complete surveys when they become too ill. • Seven patients (13%) lost to follow up. • Study underpowered to assess impact of adjuvant or neoadjuvant therapy on HRQOL due to small patient numbers.
			Patients with stage IA-IIIB NSCLC undergoing lobectomy/bilobectomy, change from baseline at 12 months post-operatively (N=42)	-0.059 (p=0.019)	
			Patients with stage IA-IIIB NSCLC undergoing lobectomy/bilobectomy, change from baseline at 24 months post-operatively (N=36)	-0.078 (p=0.001)	
Jang, 2009 [11] Canada	Adult patients with completely resected early-stage (T2N0, T1N1, or T2N1) NSCLC receiving adjuvant therapy (N=482)	**Instrument:** Q-TWiST (Method 1: arbitrary values; Method 2: EORTC-QLQ-C30, global items; Method 3: EORTC-QLQ-C30, symptom-related items; Method 4: EQ-5D-3L) **Tariff:** NR	Patients with early NSCLC, TWIST state, observation arm, method 1	1 (NR)	**Conclusions:** adjuvant chemotherapy in early-stage NSCLC improves quality-adjusted survival despite chemotherapy toxicity. **Limitations:** • Methods 2 and 3 in this study, using linearly summed QOL aggregates, are not validated methods of utility derivation, such as TTO or SG exercises, and may underestimate true utility scores.
			Patients with early NSCLC, TWIST state, observation arm, method 2	1 (NR)	
			Patients with early NSCLC, TWIST state, observation arm, method 3	1 (NR)	
			Patients with early NSCLC, TWIST state, observation arm, method 4	0.75 (NR)	
			Patients with early NSCLC, TWIST state, vinorelbine + cisplatin arm, method 1	1 (NR)	
			Patients with early NSCLC, TWIST state, vinorelbine + cisplatin arm, method 2	1 (NR)	
			Patients with early NSCLC, TWIST state, vinorelbine + cisplatin arm, method 3	1 (NR)	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
			Patients with early NSCLC, TWIST state, vinorelbine + cisplatin arm, method 4	0.75 (NR)	
			Patients with early NSCLC, toxicity state, vinorelbine + cisplatin arm, method 1	0.75 (NR)	
			Patients with early NSCLC, toxicity state, vinorelbine + cisplatin arm, method 2	0.57 (0.21)	
			Patients with early NSCLC, toxicity state, vinorelbine + cisplatin arm, method 3	0.86 (0.09)	
			Patients with early NSCLC, toxicity state, vinorelbine + cisplatin arm, method 4	0.68 (NR)	
			Patients with early NSCLC, relapse state, observation arm, method 1	0.50 (NR)	
			Patients with early NSCLC, relapse state, observation arm, method 2	0.50 (0.25)	
			Patients with early NSCLC, relapse state, observation arm, method 3	0.83 (0.10)	
			Patients with early NSCLC, relapse state, observation arm, method 4	0.60 (NR)	
			Patients with early NSCLC, relapse state, vinorelbine + cisplatin arm, method 1	0.50 (NR)	
			Patients with early NSCLC, relapse state, vinorelbine + cisplatin arm, method 2	0.50 (0.25)	
			Patients with early NSCLC, relapse state, vinorelbine + cisplatin arm, method 3	0.83 (0.10)	
			Patients with early NSCLC, relapse state, vinorelbine + cisplatin arm, method 4	0.60 (NR)	
Jang, 2010 [10]	Outpatients with stage I-IV NSCLC (N=172)	**Instrument:** EQ-5D-3L and EORTC-	Patients with NSCLC (all stages: I-IV), baseline	0.76 (0.20) [0.73, 0.78]	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
Canada		QLQ-C30 mapped to EQ-5D-3L **Tariff:** US tariff	Patients with stage I NSCLC (N=34), EQ-5D-3L (actual)	0.80 (0.18)	**Conclusions:** this study demonstrates the feasibility of converting QOL data into utilities in patients with NSCLC using linear modelling. **Limitations:** • Relatively small sample size. • Lack of a unique population to test for external validity. • Population tariffs were based on a subset of the US general population, which may not appropriately represent health preferences in Canadian patients with NSCLC. • High utility score may reflect a biased sample of higher performance status patients who were willing to complete the questionnaires.
			Patients with stage I NSCLC (N=34), EORTC-QLQ-C30 to EQ-5D-3L (mapped, predicted)	0.80 (0.14)	
			Patients with stage II NSCLC (N=16), EQ-5D-3L (actual)	0.78 (0.23)	
			Patients with stage II NSCLC (N=16), EORTC-QLQ-C30 to EQ-5D-3L (mapped, predicted)	0.80 (0.12)	
			Patients with stage III NSCLC (N=36), EQ-5D-3L (actual)	0.73 (0.23)	
			Patients with stage III NSCLC (N=36), EORTC-QLQ-C30 to EQ-5D-3L (mapped, predicted)	0.74 (0.13)	
			Patients with stage IV NSCLC (N=86), EQ-5D-3L (actual)	0.75 (0.15)	
			Patients with stage IV NSCLC (N=86), EORTC-QLQ-C30 to EQ-5D-3L (mapped, predicted)	0.77 (0.13)	
			Patients with NSCLC (all stages), relapse free, chemotherapy (N=9), EQ-5D-3L (actual)	0.76 (0.04)	
			Patients with NSCLC (all stages), relapse free, chemotherapy (N=9), EORTC-QLQ-C30 to EQ-5D-3L (mapped, predicted)	0.74 (0.06)	
			Patients with NSCLC (all stages), relapse free, post-chemotherapy (N=27), EQ-5D-3L (actual)	0.76 (0.21)	
			Patients with NSCLC (all stages), relapse free, post-chemotherapy (N=27), EORTC-QLQ-C30 to EQ-5D-3L (mapped, predicted)	0.76 (0.12)	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
			Patients with NSCLC (all stages), relapse free, no chemotherapy (N=34), EQ-5D-3L (actual)	0.77 (0.22)	
			Patients with NSCLC (all stages), relapse free, no chemotherapy (N=34), EORTC-QLQ-C30 to EQ-5D-3L (mapped, predicted)	0.80 (0.16)	
Jeppesen, 2018 [12] Denmark *(supplemented by data reported in Jeppesen et al [2017] [29])*	Patients with a diagnosis of T1-2N0M0 (localised) NSCLC treated with SBRT (N=51)	**Instrument:** EQ-5D-5L **Tariff:** Danish tariff	Patients with localised NSCLC, baseline, SBRT + CGA	0.77 (0.19)	**Conclusions:** in patients with localised NSCLC treated with SBRT, a CGA did not impact the overall quality of life, the prevalence/length of unplanned admissions, or survival. **Limitations:** • Relatively small sample size makes results difficult to interpret. • The eligibility criteria of the study did not select only a geriatric population, and this could potentially have diluted the effect of a CGA.
			Patients with localised NSCLC, baseline, SBRT alone	0.71 (0.19)	
			Patients with localised NSCLC, 5 weeks follow up, SBRT + CGA	0.75 (SE 0.03)	
			Patients with localised NSCLC, 5 weeks follow up, SBRT alone	0.70 (SE 0.03)	
			Patients with localised NSCLC, 3 months follow up, SBRT + CGA	0.77 (SE 0.04)	
			Patients with localised NSCLC, 3 months follow up, SBRT alone	0.74 (SE 0.04)	
			Patients with localised NSCLC, 6 months follow up, SBRT + CGA	0.69 (SE 0.03)	
			Patients with localised NSCLC, 6 months follow up, SBRT alone	0.67 (SE 0.03)	
			Patients with localised NSCLC, 9 months follow up, SBRT + CGA	0.75 (SE 0.04)	
			Patients with localised NSCLC, 9 months follow up, SBRT alone	0.72 (SE 0.04)	
			Patients with localised NSCLC, 12 months follow up, SBRT + CGA	0.75 (SE 0.04)	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
			Patients with localised NSCLC, 12 months follow up, SBRT alone	0.67 (SE 0.04)	
Khan, 2016 [13] UK	Patients with histologically confirmed stage I-IV NSCLC (N=98)	**Instrument:** EQ-5D (3L and 5L) and EORTC-QLQ-C30 mapped to EQ-5D (3L and 5L) **Tariff:** UK tariff [28, 30]	Patients with NSCLC, random effects model, EORTC-QLQ-C30 to EQ-5D-5L (predicted)	0.577 (0.241)	**Conclusions:** mapping algorithms developed from EQ-5D-5L appear to provide improved estimates of utilities compared with EQ-5D-3L in patients with NSCLC, particularly at poorer health states. **Limitations:** • Small sample size and relatively few health states. • Inferences should be limited to a similar NSCLC population until further evidence emerges of wider applicability across tumour types. • External validity was not possible in an independent data set. • Insufficient numbers of events were available for reliable computation of QALYs. • The values of the EQ-5D-5L were cross-walked from the EQ-5D-3L and are therefore subject to uncertainty.
			Patients with NSCLC, random effects model, EQ-5D-5L (observed)	0.572 (0.224)	
			Patients with NSCLC, beta binomial model, EORTC-QLQ-C30 to EQ-5D-5L (predicted)	0.575 (0.211)	
			Patients with NSCLC, beta binomial model, EQ-5D-5L (observed)	0.572 (0.224)	
			Patients with NSCLC, LVDM model, EORTC-QLQ-C30 to EQ-5D-5L (predicted)	0.569 (0.217)	
			Patients with NSCLC, LVDM model, EQ-5D-5L (observed)	0.572 (0.224)	
			Patients with NSCLC, random effects model, EORTC-QLQ-C30 to EQ-5D-3L (predicted)	0.523 (0.252)	
			Patients with NSCLC, random effects model, EQ-5D-3L (observed)	0.515 (0.308)	
			Patients with NSCLC, beta binomial model, EORTC-QLQ-C30 to EQ-5D-3L (predicted)	0.518 (0.183)	
			Patients with NSCLC, beta binomial model, EQ-5D-3L (observed)	0.515 (0.308)	
			Patients with NSCLC, LVDM model, EORTC-QLQ-C30 to EQ-5D-3L (predicted)	0.532 (0.252)	
			Patients with NSCLC, LVDM model, EQ-5D-3L (observed)	0.515 (0.308)	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
Kim, 2018 [14] South Korea	Adults (aged ≥19 years) from the Korean general population on behalf of patients with stage I-IV lung cancer (N=515)	**Instrument:** SG and VAS **Tariff:** NA	Stage I lung cancer, valued by proxy respondents from the Korean general public, VAS, baseline	0.48 (0.17)	**Conclusions:** findings indicate that a range of descriptions of lung cancer states can be feasibly evaluated in the South Korean population using either the VAS or SG methods. **Limitations:** • The number of scenarios was intentionally reduced to minimise the cognitive burden on participants. • Response integrity data were not collected and it is therefore not possible to analyse characteristics relating to non-response.
			Stage I lung cancer, valued by proxy respondents from the Korean general public, SG, baseline	0.66 (0.27)	
			Stage II lung cancer, valued by proxy respondents from the Korean general public, VAS, baseline	0.38 (0.17)	
			Stage II lung cancer, valued by proxy respondents from the Korean general public, SG, baseline	0.56 (0.28)	
			Stage IIIA lung cancer, valued by proxy respondents from the Korean general public, VAS, baseline	0.27 (0.17)	
			Stage IIIA lung cancer, valued by proxy respondents from the Korean general public, SG, baseline	0.45 (0.29)	
			Stage IIIB lung cancer, valued by proxy respondents from the Korean general public, VAS, baseline	0.20 (0.18)	
			Stage IIIB lung cancer, valued by proxy respondents from the Korean general public, SG, baseline	0.38 (0.29)	
			Stage IV lung cancer, valued by proxy respondents from the Korean general public, VAS, baseline	0.09 (0.18)	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
			Stage IV lung cancer, valued by proxy respondents from the Korean general public, SG, baseline	0.31 (0.30)	
			Pulmonary nodule, valued by proxy respondents from the Korean general public, VAS, baseline	0.66 (0.21)	
			Pulmonary nodule, valued by proxy respondents from the Korean general public, SG, baseline	0.83 (0.24)	
Koide, 2019 [15] Japan	Patients with stage I-III NSCLC who underwent VATS (N=24)	**Instrument:** EQ-5D-5L **Tariff:** Japanese tariff	Patients with stage I-III NSCLC, pre-operative (baseline)	0.81 (0.19)	**Conclusions:** QOL survey for NSCLC patients using EQ-5D-5L is simple and useful to identify the issue faced by the medical team; it also could predict operation time and bleeding under specific circumstances. **Limitations:** • None reported
			Patients with stage I-III NSCLC, post-operative	0.74 (0.11)	
Manser, 2006 [16] Australia	Patients with lung cancer (any stage) recruited from a tertiary multi-disciplinary lung cancer clinic (N=92)	**Instrument:** AQoL **Tariff:** NR	Patients with stage I NSCLC, baseline (N=29)	0.62 [0.43-0.87]‡	**Conclusions:** data from this study support the validity of the AQoL for use in patients with lung cancer; however, there remains some uncertainty about whether the AQoL has sufficient content validity and sensitivity to different health states for use in patients with lung cancer. **Limitations:**
			Patients with stage II NSCLC, baseline (N=15)	0.60 [0.24-0.80]‡	
			Patients with stage III NSCLC, baseline (N=22)	0.67 [0.52-0.87] ‡	
			Patients with stage IV NSCLC, baseline (N=23)	0.68 [0.54-0.82]‡	
			Patients with lung cancer, inoperable (N=42), baseline	0.66 [0.52-0.82]‡	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
			Patients with lung cancer, operable (N=49), baseline	0.67 [0.35-0.87]‡	• Potential selection bias and relatively small sample size. • Loss to follow up in the inoperable group at 3 and 6 months. • Disease-specific HRQOL questionnaire was not utilised.
			Patients with lung cancer, all patients (N=66), 3 months follow up	0.57 [0.49, 0.64]‡	
			Patients with lung cancer, operable (N=44), 3 months follow up	0.55 [0.45, 0.64]‡	
			Patients with lung cancer, inoperable (N=22), 3 months follow up	0.60 [0.49, 0.72]‡	
			Patients with lung cancer, all patients (N=59), 6 months follow up	0.59 [0.52, 0.66]‡	
			Patients with lung cancer, operable (N=43), 6 months follow up	0.59 [0.50, 0.68]‡	
			Patients with lung cancer, inoperable (N=16), 6 months follow up	0.60 [0.50, 0.70]‡	
			Patients with stage I NSCLC, surgical group, 6 months follow up (N=22)	0.67 [0.54, 0.79]‡	
			Patients with stage II-III NSCLC, surgical group, 6 months follow up (N=20)	0.55 [0.40, 0.69]‡	
			Patients with stage I-III (non-surgical) and stage IV NSCLC, 6 months follow up (N=18)	0.56 [0.46, 0.67]‡	
Naik, 2017 [17] Canada	Adult ambulatory cancer survivors, including lung cancer (N=1,759)	**Instrument:** EQ-5D-3L **Tariff:** UK, US, and Canadian tariffs	Patients with lung cancer (N=149), Canadian tariff	0.78 (SE 0.02)	**Conclusions:** this work represents the first set of health utility scores for numerous cancer sites derived using Canadian preference weights; the dataset demonstrated construct validity and health utility scores varied by general socio-demographic and clinical parameters.
			Patients with lung cancer (N=149), US tariff	0.80 (SE 0.01)	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
			Patients with lung cancer (N=149), UK tariff	0.73 (SE 0.02)	**Limitations:** • Not possible to adjust for some clinical variables in regression analysis. • Estimates presented may not necessarily be representative of cancer survivors in the Canadian community at large. • Individuals were recruited based on a convenience sampling approach.
			Patients with local/regional lung cancer (N=89), Canadian tariff	0.78 (SE 0.02)	
			Patients with distant/metastatic lung cancer (N=60), Canadian tariff	0.77 (SE 0.03)	
Rauma, 2019 [18] Finland	Patients with localised NSCLC who underwent lobectomy at a single institution between January 2006 and January 2013 (N=180)	**Instrument:** 15D **Tariff:** NR	Patients with local NSCLC, total 15D score , VATS	0.809	**Conclusions:** this study reports the surprising result that patients with NSCLC undergoing VATS had worse long-term HRQOL scores in several critical dimensions, including breathing and overall 15D score. **Limitations:** • Retrospective study design and lack of baseline HRQOL data precluded identification of actual changes in HRQOL as a consequence of the selected surgical method. • The 2-part collection of data may predispose the results to some temporal bias.
			Patients with local NSCLC, total 15D score , thoracotomy	0.851	
			Patients with local NSCLC, 15D breathing dimension , VATS	0.637	
			Patients with local NSCLC, 15D breathing dimension , thoracotomy	0.719	
			Patients with local NSCLC, 15D speaking dimension , VATS	0.942	
			Patients with local NSCLC, 15D speaking dimension , thoracotomy	0.973	
			Patients with local NSCLC, 15D usual activities dimension , VATS	0.746	
			Patients with local NSCLC, 15D usual activities dimension , thoracotomy	0.821	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
			Patients with local NSCLC, 15D mental function dimension , VATS	0.818	
			Patients with local NSCLC, 15D mental function dimension , thoracotomy	0.917	
			Patients with local NSCLC, 15D vitality dimension, VATS	0.767	
			Patients with local NSCLC, 15D vitality dimension, thoracotomy	0.824	
Sharples, 2012 [19] UK	Patients with known/suspected NSCLC, pending results of surgical staging and potentially suitable for surgical resection, with no evidence of distant metastatic disease (N=144)	**Instrument:** EQ-5D-3L **Tariff:** UK tariff (assumed from reference to Dolan et al [1997] [28])	Patients with NSCLC, baseline (day 0), EUS/EBUS (N=73)	0.81 (0.18)	**Conclusions:** taking the clinical, QOL and health resource data together, evidence from this study suggests that lung cancer staging could commence with a combined EUS/EBUS examination, followed by surgical staging if these tests are negative. **Limitations:** • Limited number of comparators. • The EQ-5D is a generic measure that is unlikely to illustrate changes in QOL that are specific to the disease course.
			Patients with NSCLC, baseline (day 0), surgical staging (N=71)	0.83 (0.14)	
			Patients with NSCLC, end of staging (day 7), EUS/EBUS (N=73)	0.78 (0.23)	
			Patients with NSCLC, end of staging (day 7), surgical staging (N=71)	0.67 (0.29)	
			Patients with NSCLC, 2 months follow up (day 61), EUS/EBUS (N=73)	0.64 (0.27)	
			Patients with NSCLC, 2 months follow up (day 61), surgical staging (N=71)	0.65 (0.26)	
			Patients with NSCLC, 6 months follow up (day 183), EUS/EBUS (N=73)	0.68 (0.30)	
			Patients with NSCLC, 6 months follow up (day 183), surgical staging (N=71)	0.67 (0.31)	
Swan, 2018 [20] US	Patients with early (I-II) or late (III-IV) stage NSCLC (N=236)	**Instrument:** SG, MAUT-based index, and FACT-U¥	Patients with early (stage I-II) NSCLC, SG, baseline	0.82 (0.16)	**Conclusions:** FACT-U shows early evidence of validity for informing economic analysis of lung cancer treatments.
			Patients with early (stage I-II) NSCLC, MAUT-based index, baseline	0.69 (0.21)	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
		Tariff: NA	Patients with early (stage I-II) NSCLC, FACT-U, baseline	0.83 (0.14)	**Limitations:** • Minorities were limited in the study sample.
			Patients with advanced (stage III-IV) NSCLC, SG, baseline	0.82 (0.13)	
			Patients with advanced (stage III-IV) NSCLC, MAUT-based index, baseline	0.60 (0.2)	
			Patients with advanced (stage III-IV) NSCLC, FACT-U, baseline	0.78 (0.14)	
Tramontano, 2015 [21] US *(supplemented by data reported in Blom et al [2020] [6])*	Patients with newly diagnosed lung cancer (stage I-IV) (N=2,396)	**Instrument:** EQ-5D-3L and SF-6D **Tariff:** NR	Patients with lung cancer, all stages, EQ-5D-3L (N=2,396)	0.78 (0.18) [0.77, 0.79]	**Conclusions:** this study generated a catalogue of community-weighted utilities applicable to societal-perspective cost-effectiveness analyses of lung cancer interventions and compared utilities based on the EQ-5D and SF-6D. **Limitations:** • None reported
			Patients with lung cancer, all stages, SF-6D (N=2,344)	0.68 (0.14) [NR]	
			Patients with stage I-II lung cancer, EQ-5D-3L (N=982)	0.80 (NR) [0.79, 0.81]	
			Patients with stage III-IV lung cancer, EQ-5D-3L (N=1,277)	0.77 (NR) [0.76, 0.78]	
Trippoli, 2001 [22] Italy	Patients with a diagnosis of NSCLC (N=92)	**Instrument:** EQ-5D-3L **Tariff:** NR	Patients with NSCLC (all; N=92)	0.58 (0.33)	**Conclusions:** the EQ-5D-3L measurements obtained from these patients will aid evaluation of the cost-utility ratio for NSCLC therapies. **Limitations:** • No detailed data about therapeutic interventions and staging were collected during the study.
			Patients with NSCLC, male (N=85)	0.58 (0.34)	
			Patients with NSCLC, female (N=7)	0.67 (0.16)	
			Patients with NSCLC, treatment with surgery (N=26)	0.56 (0.27)	
			Patients with NSCLC, no treatment with surgery (N=65)	0.59 (0.35)	
			Patients with NSCLC, treatment with chemotherapy (N=79)	0.59 (0.32)	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
			Patients with NSCLC, no treatment with chemotherapy (N=13)	0.57 (0.39)	• No disease-specific questionnaires [e.g. EORTC-QLQ-C30, FACT-L, or the LCSS) were employed.
			Patients with NSCLC, treatment with radiotherapy (N=21)	0.53 (0.30)	
			Patients with NSCLC, no treatment with radiotherapy (N=70)	0.60 (0.34)	
			Patients with NSCLC, metastasis present (N=59)	0.53 (0.36)	
			Patients with NSCLC, metastasis absent (N=32)	0.68 (0.24)	
			Patients with NSCLC, age <65 years (N=46)	0.64 (0.31)	
			Patients with NSCLC, age 65+ years (N=46)	0.54 (0.34)	
			Patients with NSCLC, time since diagnosis <12 months (N=67)	0.61 (0.34)	
			Patients with NSCLC, time since diagnosis 12+ months (N=21)	0.50 (0.30)	
Vogel, 2019 [23] US	Patients with stage I-III NSCLC receiving definitive chemo-radiation (N=43)	**Instrument:** EQ-5D (version not specified) **Tariff:** NR	Patients with stage I-III NSCLC, pre radiation	0.86	**Conclusions:** CCI was associated with multiple HRQOL outcomes in patients with locally advanced (stage I-III) NSCLC treated with definitive chemoradiation. **Limitations:**

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
			Patients with stage I-III NSCLC, post-radiation	0.83	• Relatively small sample size and highly selected patient population. • Confounding factors that may not have been adjusted for in analyses, including education level, income, and physical activity.
Witlox, 2020 [24] Netherlands	Patients with stage III NSCLC (N=174)	**Instrument:** EQ-5D-3L **Tariff:** Dutch tariff	Patients with stage III NSCLC, prophylactic cranial irradiation arm, baseline	0.80	**Conclusions:** a statistically significant nor a clinically relevant impact of prophylactic cranial irradiation on HRQOL was not observed in this study in patients with stage III NSCLC. **Limitations:** • Patients who developed symptomatic brain metastases may have dropped out of the analysis and thus HRQOL might be potentially overestimated overall. • The NVALT-11/DLCRG-02 trial was not powered to detect a statistically significant difference between the study arms, as HRQOL was a secondary endpoint.
			Patients with stage III NSCLC, observation arm, baseline	0.79	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
Wolff, 2018 [25] Netherlands	Patients with stage I NSCLC treated with either SBRT or surgery (N=302)	**Instrument:** EORTC-QLQ-C30 mapped to EQ-5D-3L (published algorithm by Longworth et al [2014] [31]) **Tariff:** UK tariff (assumed from reference to Dolan et al [1997] [28])	Patients with stage I NSCLC, treatment difference at baseline, SBRT vs surgery	0.071 [0.017, 0.128]	**Conclusions:** this study shows that there is no clinically meaningful difference in health utility between patients with surgically treated early-stage NSCLC and patients treated with SBRT. **Limitations:** • It was not possible to study the impact of treatment toxicities on health utility. • Fourteen patients were censored at the start of adjuvant treatment or when a recurrence was detected.
			Patients with stage I NSCLC, mean 1-year treatment difference, SBRT vs surgery	0.026 [-0.028, 0.080]	
Yang, 2014 [27] Taiwan	Patients with NSCLC and free from other malignancies during the period from January 2005 to December 2011 (N=518)	**Instrument:** EQ-5D-3L **Tariff:** Taiwanese tariff	Patients with stage I NSCLC, performance status 0-1, operable (N=275)	0.86 (0.17)	**Conclusions:** the utility gained from surgical operation for operable lung cancer is substantial, even after adjustment for lead-time bias. **Limitations:** • QOL and survival of patients might be affected by major chronic diseases. • QOL measurements from some individuals were performed repeatedly. • The estimation of QALE would have been more accurate if the QOL of every patient
			Patients with stage II NSCLC, performance status 0-1, operable (N=275)	0.83 (0.17)	
			Patients with stage III NSCLC, performance status 0-1, operable (N=275)	0.83 (0.17)	
			Patients with stage III NSCLC, performance status 0-1, inoperable (N=243)	0.73 (0.25)	
			Patients with stage I NSCLC, performance status 0-4, operable (N=281)	0.85 (0.17)	
			Patients with stage II NSCLC, performance status 0-4, operable (N=281)	0.83 (0.17)	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
			Patients with stage III NSCLC, performance status 0-4, operable (N=281)	0.83 (0.16)	in the cohort repeatedly during the follow-up period.
			Patients with stage III NSCLC, performance status 0-4, inoperable (N=250)	0.72 (0.25)	
			Patients with operable NSCLC, performance status 0-1 (N=275), male, age ≤54 years	0.86 (0.15)	
			Patients with operable NSCLC, performance status 0-1 (N=275), male, age 55-74 years	0.86 (0.16)	
			Patients with operable NSCLC, performance status 0-1 (N=275), male, age ≥75 years	0.77 (0.19)	
			Patients with operable NSCLC, performance status 0-1 (N=275), female, age ≤54 years	0.86 (0.16)	
			Patients with operable NSCLC, performance status 0-1 (N=275), female, age 55-74 years	0.82 (0.17)	
			Patients with operable NSCLC, performance status 0-1 (N=275), female, age ≥75 years	0.72 (0.23)	
			Patients with operable NSCLC, performance status 0-4 (N=281), male, age ≤54 years	0.86 (0.15)	
			Patients with operable NSCLC, performance status 0-4 (N=281), male, age 55-74 years	0.86 (0.16)	
			Patients with operable NSCLC, performance status 0-4 (N=281), male, age ≥75 years	0.77 (0.19)	
			Patients with operable NSCLC, performance status 0-4 (N=281), female, age ≤54 years	0.86 (0.16)	
			Patients with operable NSCLC, performance status 0-4 (N=281), female, age 55-74 years	0.82 (0.17)	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
			Patients with operable NSCLC, performance status 0-4 (N=281), female, age ≥75 years	0.72 (0.23)	
Yang, 2019 [26] Taiwan	Patients with lung cancer (any stage) visiting the author's hospital (N=1,715)	**Instrument:** EQ-5D-3L **Tariff:** Taiwanese tariff	Patients with stage I-IIIA squamous NSCLC, age <65 years (N=46)	0.88 (SE 0.02)	**Conclusions:** this 7-year real-world survey provided detailed EQ-5D estimates of health utility, which could be used for future cost-effectiveness analysis for treatments of lung cancer; compared with patients undergoing second-line chemotherapy, those receiving targeted therapy had higher utility values. **Limitations:** • Detailed AEs were not included in each measurement, which may have a considerable impact on QOL, in the mixed model analysis. • Most participants were from outpatient departments, and thus the utility values were likely to be overestimated. • QOL measurements were not performed in a predefined period.
			Patients with stage I-IIIA non-squamous NSCLC, age <65 years (N=350)	0.90 (SE 0.01)	
			Patients with stage I-IIIA squamous NSCLC, age ≥65 years (N=68)	0.85 (SE 0.02)	
			Patients with stage I-IIIA non-squamous NSCLC, age ≥65 years (N=260)	0.86 (SE 0.01)	
			Patients with stage IIIB-IV squamous NSCLC, age <65 years (N=46)	0.84 (SE 0.03)	
			Patients with stage IIIB-IV non-squamous NSCLC, age <65 years (N=476)	0.85 (SE 0.01)	
			Patients with stage IIIB-IV squamous NSCLC, age ≥65 years (N=66)	0.73 (SE 0.03)	
			Patients with stage IIIB-IV non-squamous NSCLC, age ≥65 years (N=321)	0.81 (SE 0.01)	
June 2022 update (N=2)					

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
Mahal, 2021 [3] US	Patients who were treated for a primary stage I-III tumour (prostate, breast, lung) with valid dates of diagnosis and death and who did not have a second cancer diagnosed before their follow-up survey (N=67 [patients with lung cancer only])	**Instrument:** SF-6D **Tariff:** NA (study used an algorithm to calculate utilities from SF-12 and SF-36)	Early era lung cancer patients (treated 1998–2003); baseline (N=67)	0.72 (0.14)	**Conclusions:** Older patients treated for prostate, breast, or lung cancer in the 'Late Era' reported similar outcomes of changes in HRQOL compared to 'Early Era' patients. That is, as advancements in cancer care have become more successful (and potentially more intense), the quality-of-life of patients undergoing contemporary therapy has not been impacted. This finding perhaps highlights significant improvements in supportive care services. **Limitations:** • The study analysed only patients who were enrolled in the Medicare Advantage plan and thus part of the Medicare Health Outcomes Survey. It is possible that Medicare Advantage enrolees are healthier than fee-for-service beneficiaries, though others have shown equivalence. • The researchers were unable to assess the specific treatments received by patients. The SEER-MHOS combined database does not include claims; therefore, only the SEER treatment variables were available, which are general. • Due to limitations of the dataset, it was not possible to assess HRQOL/utilities more than two years after cancer treatment and
			Early era lung cancer patients (treated 1998–2003); change from baseline at follow-up (N=62)	–0.07 (0.14)	
			Late era lung cancer patients (treated 2006–2011); baseline (N=67)	0.74 (0.14)	
			Late era lung cancer patients (treated 2006–2011); change from baseline at follow-up (N=62)	–0.07 (0.12)	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
					it is possible that trends in health utility changes after two years differ from those within two years. • The study was limited by the small sample size of patients who had completed a survey both pre-cancer diagnosis and post cancer treatment. • A calliper was not used in the propensity score matching algorithm. • There is potential for residual confounding. Many standardised mean differences presented in this study were large due to the sample size. Regression adjustment to mitigate residual imbalance was not conducted.
Sigel, 2022 [2] US	Patients with stage I NSCLC with major comorbid illness (N=15,537)	**Instrument:** SF-6D **Tariff:** NA (study used an algorithm to calculate utilities from SF-12 and SF-36)	Mean utility from SEER-MHOS data for stage I NSCLC patients (N=1,292)	0.77	**Conclusions:** Simulation modelling approaches were used to estimate the QALE gains associated with different treatment approaches for stage I NSCLC patients according to age, sex, tumour size and histologic subtype and comorbidity profile. It was found that more aggressive surgical approaches were associated with the greatest projected life year gains in most scenarios although older patients and those with greater comorbid burden often benefited equally from less aggressive strategies. These results may be useful for guiding future comparative research.
			Annual utility decline for participants at risk of stage I lung cancer (N=NR)	0.017	

Study, country	Population (sample size)	Method used to derive utilities	Health states	HSUV (SD) [95% CI]	Summary of reported study conclusions and limitations
					Limitations: • Limitations in the available randomised data for comparison of the treatment modalities are included in this analysis. Direct experimental comparison data for segmentectomy, wedge resection, and SBRT are even more limited. • The ascertainment of comorbidity status from the cancer cohorts relied on diagnostic codes, which may have limited accuracy and could not be used to assess disease severity. • The model does not reflect changes in lung cancer survival associated with sociodemographic or geographic regional differences, although US population-based data was used for much of the parameterisation. • Accepted clinically meaningful differences in survival have not been well established for stage I lung cancer treatments.

Colour coding: GREEN: health states relevant to patients with stage II/III(A) disease; ORANGE: uncertainty in the method used to derive utilities (instrument and/or social tariff unclear); RED: intervention-specific health state where surgery +/- adjuvant chemotherapy is not used (e.g., relates to radiotherapy use); BLUE: both GREEN and RED criteria apply.
Abbreviations: 15D - 15 Dimensions, AE - adverse event, AQoL - Assessment of Quality of Life, CCI - Charlson Comorbidity Index, CI - confidence interval, CGA - comprehensive geriatric assessment, EBUS - endobronchial ultrasound, EORTC-QLQ-C30 - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, EQ-5D (3L/5L) - European Quality of Life-5 Dimensions (3 Level/5 Level version), EUS - endoscopic ultrasound, FACT-L - Functional Assessment of Cancer Therapy – Lung, FACT-U - Functional Assessment of Cancer Therapy - Lung Utility Index, HRQOL - health-related quality of life, HSUV - health state utility value, IQR - interquartile range, LCSS - Lung Cancer Symptom Scale, LVDM - Limited Variable Dependent Mixture, MAUT - multi-attribute utility theory,

NA - not applicable, NR - not reported, NSCLC - non-small cell lung cancer, QALE - quality adjusted life expectancy, QALY - quality adjusted life year, QOL - quality of life, SBRT - stereotactic body radiation therapy, SD - standard deviation, SE - standard error, SF-6D - Short Form-6 Dimensions, SG - standard gamble, TTO - time trade off, UK - United Kingdom, US - United States, VATS - video-assisted thoracoscopic surgery, VAS - visual analogue scale.

† Individuals contributing to pooled value for all stages: Stage I-II: N=1,510; Stage III-IV: N=4,703.

¥ The FACT-U was constructed with two methods: (i) MAUT, where a VAS–based index was transformed to SG; and (ii) an unweighted index, where items were summed, normalised to a 0 to 1.0 scale, and the result transformed to a scale length equivalent to the VAS or SG MAUT-based model on a Dead to Full Health scale.

‡ Median [IQR].

1.4 Quality assessment and generalizability of estimates

IMpower010 did not collect patient reported outcomes, therefore literature was used to estimate health state values in the model.

During data extraction, the relevance of utilities, and the quality of the studies generating them were assessed and recorded and the quality of any mapping algorithms examined. This process was in line with the recommendations in the NICE technical support documents (TSDs) 8-10[32].

In particular, the following issues were addressed:

- Whether response rates, loss to follow-up, or missing data were likely to threaten the validity of the utility estimate
- Whether the selection criteria yielded a population similar to that being modelled
- Whether utility incorporated decrement for quality of life loss from adverse events (AEs)

The quality assessment highlighted a number of limitations associated with the utility values. In particular, absence of information regarding the patient recruitment process, response rates to instruments, and missing data which all in turn were likely to restrict the usefulness of the studies for informing economic evaluations. Commonly reported limitations across the studies included*:

- relatively small sample sizes (N=12) [1, 3, 7-10, 12, 13, 16, 23-25]
- limited generalisability of results beyond the study setting (N=9) [1, 5, 7, 10, 13, 17, 20, 23, 26]
- potential over-estimation of HRQOL due to non-responder bias and/or loss to follow up (N=6) [8, 9, 14, 16, 17, 24]
- lack of external validation of results (N=3) [1, 10, 13]

*Conference abstracts were not quality assessed due to limited reporting.

Four studies fully met the requirements of the NICE reference case [8, 13, 17, 19]; that is, utilities were derived directly from patients using the preferred EQ-5D-3L instrument and that health states were valued using UK societal preferences elicited using the direct time trade off (TTO) method [33]. These studies are likely to be considered most appropriate for informing economic evaluations in a UK setting. For the remaining 23 studies, the reference case requirements were either clearly not met (N=18; primarily due to use of non-UK tariffs and/or instruments other than the EQ-5D) [2-7, 9, 10, 12, 14-16, 18, 20, 24-27] or it was unclear if they were met due to limited reporting (N=5) [1, 11, 21-23].

Three Danish studies were identified in the global SLR. Two of the studies included EQ-5D-5L, and the last one included EQ-5D-3L, all assumed using Danish tariffs. However, it is not good practice to use differing methods across states, whether that be differing questionnaires EQ-5D-3L/EQ-5D-5L or differing tariffs (UK and DK) as these leads to a lack of validity within the values applied to each health state. As no DK utilities were identified that could be applied to all states, UK utilities were used instead.

1.5 Additional HRQoL data

As part of the evidence generation a series of health-technology assessment (HTA)-compliant systematic literature reviews (SLRs) were conducted to identify the following published evidence in early-stage NSCLC:

- Economic evaluations of relevant treatments
- Cost/resource use data

The search below is the method and findings from the review of economic evaluations. These included some additional HRQoL data relevant for the included health states.

1.5.1 Search strategy

The following electronic databases were searched via the Ovid platform on the 18th of March 2021 and the 4th of July 2022:

- Embase, 1974 to 2022 July 01
- MEDLINE, 1946 to July 1, 2022, including:
  - MEDLINE Epub Ahead of Print
  - MEDLINE In-Process, In-Data-Review & Other Non-Indexed Citations
  - MEDLINE Daily
- EBM Reviews, incorporating:
  - Cochrane Database of Systematic Reviews, 2005 to 29 June, 2022
  - American College of Physicians (ACP) Journal Club, 1991 to June 2022
  - Database of Abstracts of Reviews of Effects (DARE), 1st Quarter 2016
  - Cochrane Clinical Answers, June 2022
  - Cochrane Central Register of Controlled Trials (CENTRAL), May 2022
  - Cochrane Methodology Register, 3rd Quarter 2012
  - HTA database, 4th Quarter 2016
  - National Health Service Economic Evaluation Database (NHS EED), 1st Quarter 2016
- EconLit, 1886 to June 23, 2022

The EBM databases, DARE, NHS EED, and HTA, which are not updated to the present day, were also searched via the University of York Centre for Reviews and Dissemination (CRD) website: https://www.crd.york.ac.uk/. Furthermore, the same supplementary sources as for the HRQoL SLR (section 1.1) was used together with additional databases/websites:

- Health Economics Research Centre
- Cost-effectiveness analysis (CEA) Registry

The eligibility criteria applied throughout the economic evaluation SLR are summarised in Table 57.

Table 57. Eligibility criteria, Economic evaluation SLR

Criteria	Include	Exclude
POPULATION	Patients with early-stage NSCLC (resectable; stage 0/I/II/III) receiving treatment in the adjuvant or neoadjuvant treatment settings – no restriction with regard to patient age or mutation status *Note: the primary population of interest was patients with stage II-III resectable disease; however, studies considering patients with stage I-III disease were considered eligible during the screening process to assess the extent of evidence available.*	• Advanced/metastatic (stage IV) NSCLC • Mixed populations where a breakdown of data for early-stage NSCLC is not provided
INTERVENTION & COMPARATORS	***Intervention:*** atezolizumab ***Comparators:*** • Platinum-based chemotherapy (alone or in combination with other agents)	Diagnostic interventions (e.g. screening, genetic testing)

	• Pembrolizumab • Durvalumab • Nivolumab • Cemiplimab • Avelumab • Tegafur +/- uracil (UFT) • Osimertinib • Erlotinib • Gefitinib • Afatinib • Pemetrexed • Docetaxel • Gemcitabine • Vinorelbine • Etoposide • Radiotherapy • Surgery • Supportive care (including imaging [e.g. CT scans to assess recurrence])	
OUTCOMES	• Summary costs and health outcomes (e.g. QALYs, LYG) • Cost-effectiveness estimates (e.g. ICERs): base case and sensitivity analyses • Assumptions underpinning analysis • Model structure and summary (including perspective, time horizon, and discounting) • Sources of key model inputs • Key cost drivers • Transition probabilities	Outcomes not listed in "include" column
STUDY DESIGN	• Cost-effectiveness analyses • Cost-utility analyses • Cost-benefit analyses • Cost-minimisation analyses	• Reviews/editorials† • Case reports • Pharmacokinetic studies • Animal/*in vitro* studies
GEOGRAPHY	No restriction; however, i8 countries (UK, France, Spain, Canada, Australia, Brazil, Germany and Italy), China, South Korea, Japan, and the US were primary territories of interest	-
PUBLICATION DATE	No restriction	-
LANGUAGE	No restriction; English language publications or non-English language publications with an English abstract were of primary interest.	-

Abbreviations: CT, computed tomography; ICER, incremental cost-effectiveness ratio; LYG, life year gained; NSCLC, non-small cell lung cancer; QALY, quality adjusted life year; UK, United Kingdom; US, United States.

†The reference lists of any relevant review publications were checked to ensure any relevant primary studies were considered for inclusion.

1.5.2 Systematic selection of studies

Original review (March 2021)

Electronic searches of the following databases were conducted on the 18th of March 2021 via the Ovid platform: Embase, MEDLINE (including Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, and Daily), EBM Reviews (incorporating: the Cochrane Database of Systematic Reviews; the ACP Journal Club; DARE; Cochrane Clinical Answers; Cochrane Central Register of Controlled Trials; the Cochrane Methodology Register; the HTA database; and NHS EED), and EconLit. Search algorithms reported in Table 58, Table 59, Table 60, and Table 61. The electronic databases searches were supplemented by hand searching of reference lists of included studies, relevant conference proceedings (last 3 years availability), and additional grey literature sources.

The electronic searches identified a total of 1,215 citations. After removal of 127 duplicates, 1,088 citations were screened on the basis of title and abstract. A total of 66 were considered to be potentially relevant and were obtained for full text review. At this stage, a further 46 citations were excluded. Hand searching of the grey literature yielded 15 additional publications (published analyses, N=14; NICE guidelines, N=1). This resulted in a total of 35 publications for final inclusion in the economic evaluation SLR (full publications, N=24; conference abstracts, N=10; NICE guidelines, N=1b).

July 2022 update

Electronic searches of the following databases were conducted on the 4th of July 2022 via the Ovid platform: Embase, MEDLINE (including Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, and Daily), and EBM Reviews (incorporating: the Cochrane Database of Systematic Reviews; the ACP Journal Club; Cochrane Clinical Answers; and Cochrane Central Register of Controlled Trials). Search algorithms reported in Table 62, Table 63, Table 64, and Table 65. The electronic databases searches were supplemented by hand searching of reference lists of included studies, relevant conference proceedings (conducted after the original search to June 2022), and additional grey literature sources.

The electronic database search identified 287 citations. After the removal of 43 duplicates from the current search and seven duplicates of the original search (March 2021), 237 citations were screened on the basis of title and abstract. A total of nine publications were deemed potentially relevant and were obtained for full text review. At full publication review stage, a further three publications were excluded. Hand searching yielded five additional studies. This resulted in a total of 11 publications for final inclusion in the economic evaluations SLR update (full publications, N=4; abstracts, N=5; HTA submissions, N=2).

Search algoritm

Original Review (March 2021)

Embase 1974 to 2021 March 17
Accessed 18th March 2021

Table 58. Embase, Original review March 2021

	Searches	Results
1	exp lung non small cell cancer/ or exp non small cell lung cancer/	107597
2	((lung* or pulmonary) adj2 (carcinom* neoplasm* or cancer* or tumo?r* or malignan*)).mp.	378624
3	non.mp.	3480438

[b] In the data extraction table, the NG122 NICE guideline has been extracted on two separate rows, one for the cost-utility of routine imaging and one for the cost-utility of treatment for NSCLC.

	Searches	Results
4	2 and 3	164867
5	NSCLC.mp.	88384
6	1 or 4 or 5	200123
7	(resectable or resected).mp.	129642
8	(early or early-stage or early stage).mp.	2216301
9	("stage 0" or "stage 1" or "stage I" or "stage 2" or "stage II" or "stage 3*" or "stage III*").mp.	205002
10	or/7-9	2487366
11	6 and 10	47446
12	adjuvant therapy/	59096
13	neoadjuvant therapy/	13398
14	neoadjuvant chemotherapy/ or adjuvant chemotherapy/ or chemotherapy/	208528
15	radiotherapy/ or adjuvant radiotherapy/	156884
16	lung surgery/ or cancer surgery/	310745
17	carboplatin/ or cisplatin/ or platinum/	254424
18	(platinum adj2 (chemo* or antineoplastic* or compound* or formulation*)).mp.	16893
19	(cisplatin or Cisplatinum or platamin* or neoplatin* or cismaplat* or CDDP).mp.	200677
20	(carboplatin or paraplatin*).mp.	74737
21	tegafur/	6755
22	(tegafur or fl?orafur* or sunfural* or furflucil* or futraful* or lifril*).mp.	13350
23	UFT/ or UFT*.mp.	5226
24	atezolizumab/	6616
25	(atezolizumab or Tecentriq*).mp.	6967
26	durvalumab/	4656
27	(durvalumab or imfinzi*).mp.	4816
28	cemiplimab/	468
29	(cemiplimab or libtayo*).mp.	501
30	avelumab/	2944
31	(avelumab or bavencio*).mp.	3080
32	nivolumab/	21009
33	(nivolumab or opdivo*).mp.	22059
34	pembrolizumab/	18821
35	(pembrolizumab or keytruda*).mp.	19815
36	osimertinib/	3806
37	(osimertinib or Tagrisso*).mp.	3994
38	erlotinib/	27934

	Searches	Results
39	(erlotinib or tarceva*).mp.	28895
40	gefitinib/	25271
41	(gefitinib or iressa*).mp.	26225
42	afatinib/	5702
43	(afatinib or gi?otrif*).mp.	5942
44	docetaxel/	61272
45	(docetaxel or taxotere*).mp.	63440
46	gemcitabine/	59642
47	(gemcitabine or gemzar*).mp.	61879
48	etoposide/	90029
49	(etoposide or Vepesid*).mp.	93401
50	pemetrexed/	14947
51	(pemetrexed or Alimta*).mp.	15512
52	vinorelbine tartrate/	3154
53	(vinorelbine or navelbine*).mp.	18958
54	(supportive care or BSC).mp.	34954
55	or/12-54	1023510
56	health economics/	33449
57	exp economic evaluation/	316964
58	exp "health care cost"/	300976
59	exp fee/	40853
60	budget/	30362
61	funding/	51715
62	budget*.ti,ab.	40692
63	cost*.ti,ab.	871657
64	(economic* or pharmaco?economic*).ti.	64630
65	(price* or pricing*).ti,ab.	61006
66	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	239551
67	(financ* or fee or fees).ti,ab.	176371
68	(value adj2 (money or monetary)).ti,ab.	3469
69	or/56-68	1375869
70	11 and 55 and 69	890

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) 1946 to March 17, 2021

Accessed 18th March 2021

Table 59. Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R), Original review March 2021

	Searches	Results
1	exp Carcinoma, Non-Small-Cell Lung/	56016
2	((lung* or pulmonary) adj2 (carcinom* neoplasm* or cancer* or tumo?r* or malignan*)).mp.	190753
3	non.mp.	9608687
4	2 and 3	114637
5	NSCLC.mp.	47108
6	1 or 4 or 5	123598
7	(resectable or resected).mp.	84623
8	(early or early-stage or early stage).mp.	1633295
9	("stage 0" or "stage 1" or "stage I" or "stage 2" or "stage II" or "stage 3*" or "stage III*").mp.	114935
10	or/7-9	1797938
11	6 and 10	25731
12	Chemotherapy, Adjuvant/	41784
13	Neoadjuvant Therapy/	21923
14	Drug Therapy/ or Antibodies, Monoclonal/	221915
15	Radiotherapy/ or Radiotherapy, Adjuvant/ or Chemoradiotherapy, Adjuvant/	68606
16	surgical oncology/ or thoracic surgery/	13351
17	Platinum/ or Carboplatin/ or Cisplatin/	70309
18	(platinum adj2 (chemo* or antineoplastic* or compound* or formulation*)).mp.	11094
19	(cisplatin or Cisplatinum or platamin* or neoplatin* or cismaplat* or CDDP).mp.	80097
20	(carboplatin or paraplatin*).mp.	18301
21	Tegafur/	5803
22	(tegafur or fl?orafur* or sunfural* or furflucil* or futraful* or lifril*).mp.	6431
23	Uracil/ or UFT*.mp.	11583
24	(atezolizumab or Tecentriq*).mp.	1480
25	(durvalumab or imfinzi*).mp.	737
26	(cemiplimab or libtayo*).mp.	120
27	(avelumab or bavencio*).mp.	563
28	Nivolumab/	2994
29	(nivolumab or opdivo*).mp.	6235
30	(pembrolizumab or keytruda*).mp.	5179
31	(osimertinib or Tagrisso*).mp.	1367
32	Erlotinib Hydrochloride/	4005

	Searches	Results
33	(erlotinib or tarceva*).mp.	7119
34	Gefitinib/	4561
35	(gefitinib or iressa*).mp.	7566
36	Afatinib/	724
37	(afatinib or gi?otrif*).mp.	1548
38	Docetaxel/	10922
39	(docetaxel or taxotere*).mp.	17550
40	(gemcitabine or gemzar*).mp.	17934
41	Etoposide/	16903
42	(etoposide or Vepesid*).mp.	26082
43	Pemetrexed/	2142
44	(pemetrexed or Alimta*).mp.	3655
45	Vinorelbine/	2731
46	(vinorelbine or navelbine*).mp.	4242
47	(supportive care or BSC).mp.	19172
48	or/12-47	527906
49	"Health Care Economics and Organizations"/ or Economics/	27300
50	exp Cost-Benefit Analysis/	83738
51	Health Care Costs/	40907
52	exp "Fees and Charges"/	30616
53	Budgets/	11403
54	"Value of Life"/	5736
55	budget*.ti,ab.	30648
56	cost*.ti,ab.	643364
57	(economic* or pharmaco?economic*).ti.	51184
58	(price* or pricing*).ti,ab.	42927
59	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	170735
60	(financ* or fee or fees).ti,ab.	128835
61	(value adj2 (money or monetary)).ti,ab.	2528
62	or/49-61	883382
63	11 and 48 and 62	164

EBM Reviews - Cochrane Database of Systematic Reviews 2005 to March 3, 2021, **EBM Reviews - ACP Journal Club** 1991 to February 2021, **EBM Reviews - Database of Abstracts of Reviews of Effects** 1st Quarter 2016, **EBM Reviews - Cochrane Clinical Answers** February 2021, **EBM Reviews - Cochrane Central Register of Controlled Trials** February 2021, **EBM Reviews - Cochrane Methodology Register** 3rd Quarter 2012, **EBM Reviews - Health Technology Assessment** 4th Quarter 2016, **EBM Reviews - NHS Economic Evaluation Database** 1st Quarter 2016
Accessed 18th March 2021

Table 60. EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - ACP Journal Club, EBM Reviews - Database of Abstracts of Reviews of Effects, EBM Reviews - Cochrane Clinical Answers, EBM Reviews - Cochrane Central Register of Controlled Trials, EBM Reviews - Cochrane Methodology Register, EBM Reviews - Health Technology Assessment, EBM Reviews - NHS Economic Evaluation Database, Original review March 2021

	Searches	Results
1	exp Carcinoma, Non-Small-Cell Lung/	4694
2	((lung* or pulmonary) adj2 (carcinom* neoplasm* or cancer* or tumo?r* or malignan*)).mp.	24499
3	non.mp.	266659
4	2 and 3	16349
5	NSCLC.mp.	10335
6	1 or 4 or 5	17277
7	(resectable or resected).mp.	8864
8	(early or early-stage or early stage).mp.	140794
9	("stage 0" or "stage 1" or "stage I" or "stage 2" or "stage II" or "stage 3*" or "stage III*").mp.	28713
10	or/7-9	171216
11	6 and 10	6258
12	Chemotherapy, Adjuvant/	4029
13	Neoadjuvant Therapy/	1252
14	Drug Therapy/ or Antibodies, Monoclonal/	7188
15	Radiotherapy/ or Radiotherapy, Adjuvant/ or Chemoradiotherapy, Adjuvant/	2480
16	surgical oncology/ or thoracic surgery/	190
17	Platinum/ or Carboplatin/ or Cisplatin/	7066
18	(platinum adj2 (chemo* or antineoplastic* or compound* or formulation*)).mp.	3576
19	(cisplatin or Cisplatinum or platamin* or neoplatin* or cismaplat* or CDDP).mp.	16026
20	(carboplatin or paraplatin*).mp.	7884
21	Tegafur/	602
22	(tegafur or fl?orafur* or sunfural* or furflucil* or futraful* or lifril*).mp.	1116
23	Uracil/ or UFT*.mp.	769
24	(atezolizumab or Tecentriq*).mp.	896
25	(durvalumab or imfinzi*).mp.	646

	Searches	Results
26	(cemiplimab or libtayo*).mp.	46
27	(avelumab or bavencio*).mp.	242
28	Nivolumab/	458
29	(nivolumab or opdivo*).mp.	2062
30	(pembrolizumab or keytruda*).mp.	1830
31	(osimertinib or Tagrisso*).mp.	269
32	Erlotinib Hydrochloride/	550
33	(erlotinib or tarceva*).mp.	1945
34	Gefitinib/	311
35	(gefitinib or iressa*).mp.	1229
36	Afatinib/	62
37	(afatinib or gi?otrif*).mp.	465
38	Docetaxel/	2133
39	(docetaxel or taxotere*).mp.	8200
40	(gemcitabine or gemzar*).mp.	6617
41	Etoposide/	1807
42	(etoposide or Vepesid*).mp.	4548
43	Pemetrexed/	659
44	(pemetrexed or Alimta*).mp.	2289
45	Vinorelbine/	556
46	(vinorelbine or navelbine*).mp.	2095
47	(supportive care or BSC).mp.	4997
48	or/12-47	56212
49	"Health Care Economics and Organizations"/ or Economics/	69
50	exp Cost-Benefit Analysis/	19415
51	Health Care Costs/	5012
52	exp "Fees and Charges"/	520
53	Budgets/	73
54	"Value of Life"/	148
55	budget*.ti,ab.	1365
56	cost*.ti,ab.	86718
57	(economic* or pharmaco?economic*).ti.	7732
58	(price* or pricing*).ti,ab.	2661
59	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	31654
60	(financ* or fee or fees).ti,ab.	8406

	Searches	Results
61	(value adj2 (money or monetary)).ti,ab.	373
62	or/49-61	100564
63	11 and 48 and 62	121

EconLit 1886 to March 11, 2021
Accessed 18th March 2021

Table 61. Econlit, Original review March 2021

	Searches	Results
1	((lung* or pulmonary) adj2 (carcinom* neoplasm* or cancer* or tumo?r* or malignan*)).mp.	141
2	non.mp.	167153
3	1 and 2	40

July 2022 update

Embase 1974 to 2022 July 01
Accessed 4th July 2022

Table 62. Embase, July 2022 update

#	Searches	Results
1	exp lung non small cell cancer/ or exp non small cell lung cancer/	130197
2	((lung* or pulmonary) adj2 (carcinom* neoplasm* or cancer* or tumo?r* or malignan*)).mp.	416976
3	non.mp.	3829138
4	2 and 3	186617
5	NSCLC.mp.	99997
6	1 or 4 or 5	226766
7	(resectable or resected).mp.	138610
8	(early or early-stage or early stage).mp.	2397338
9	("stage 0" or "stage 1" or "stage I" or "stage 2" or "stage II" or "stage 3*" or "stage III*").mp.	224097
10	or/7-9	2690566
11	6 and 10	52797
12	adjuvant therapy/	63142
13	neoadjuvant therapy/	18016
14	neoadjuvant chemotherapy/ or adjuvant chemotherapy/ or chemotherapy/	226964
15	radiotherapy/ or adjuvant radiotherapy/	168897
16	lung surgery/ or cancer surgery/	354168
17	carboplatin/ or cisplatin/ or platinum/	275251
18	(platinum adj2 (chemo* or antineoplastic* or compound* or formulation*)).mp.	19239
19	(cisplatin or Cisplatinum or platamin* or neoplatin* or cismaplat* or CDDP).mp.	215542
20	(carboplatin or paraplatin*).mp.	82057
21	tegafur/	6915
22	(tegafur or fl?orafur* or sunfural* or furflucil* or futraful* or lifril*).mp.	14355
23	UFT/ or UFT*.mp.	5368
24	atezolizumab/	10514
25	(atezolizumab or Tecentriq*).mp.	11032
26	durvalumab/	7228
27	(durvalumab or imfinzi*).mp.	7469
28	cemiplimab/	1044
29	(cemiplimab or libtayo*).mp.	1099
30	avelumab/	4589
31	(avelumab or bavencio*).mp.	4772

32	nivolumab/	29260
33	(nivolumab or opdivo*).mp.	30495
34	pembrolizumab/	27402
35	(pembrolizumab or keytruda*).mp.	28718
36	osimertinib/	5573
37	(osimertinib or Tagrisso*).mp.	5819
38	erlotinib/	30005
39	(erlotinib or tarceva*).mp.	31033
40	gefitinib/	27205
41	(gefitinib or iressa*).mp.	28212
42	afatinib/	6990
43	(afatinib or gi?otrif*).mp.	7239
44	docetaxel/	67146
45	(docetaxel or taxotere*).mp.	69438
46	gemcitabine/	65844
47	(gemcitabine or gemzar*).mp.	68267
48	etoposide/	95623
49	(etoposide or Vepesid*).mp.	99519
50	pemetrexed/	16971
51	(pemetrexed or Alimta*).mp.	17583
52	vinorelbine tartrate/	4316
53	(vinorelbine or navelbine*).mp.	20088
54	(supportive care or BSC).mp.	39413
55	or/12-54	1128849
56	health economics/	34420
57	exp economic evaluation/	335556
58	exp "health care cost"/	320680
59	exp fee/	42351
60	budget/	31744
61	funding/	66715
62	budget*.ti,ab.	43829
63	cost*.ti,ab.	956720
64	(economic* or pharmaco?economic*).ti.	70171
65	(price* or pricing*).ti,ab.	66622
66	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	262547
67	(financ* or fee or fees).ti,ab.	198287
68	(value adj2 (money or monetary)).ti,ab.	3761
69	or/56-68	1507157

70	11 and 55 and 69	1123
71	limit 70 to yr="2021 -Current"	228

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to July 01, 2022

Accessed 4th July 2022

Table 63. Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions, July 2022 update

#	Searches	Results
1	exp Carcinoma, Non-Small-Cell Lung/	65178
2	((lung* or pulmonary) adj2 (carcinom* neoplasm* or cancer* or tumo?r* or malignan*)).mp.	211748
3	non.mp.	10268277
4	2 and 3	128493
5	NSCLC.mp.	54682
6	1 or 4 or 5	138380
7	(resectable or resected).mp.	90947
8	(early or early-stage or early stage).mp.	1777922
9	("stage 0" or "stage 1" or "stage I" or "stage 2" or "stage II" or "stage 3*" or "stage III*").mp.	125173
10	or/7-9	1955879
11	6 and 10	28727
12	Chemotherapy, Adjuvant/	44687
13	Neoadjuvant Therapy/	26209
14	Drug Therapy/ or Antibodies, Monoclonal/	228316
15	Radiotherapy/ or Radiotherapy, Adjuvant/ or Chemoradiotherapy, Adjuvant/	71253
16	surgical oncology/ or thoracic surgery/	14103
17	Platinum/ or Carboplatin/ or Cisplatin/	75119
18	(platinum adj2 (chemo* or antineoplastic* or compound* or formulation*)).mp.	12466
19	(cisplatin or Cisplatinum or platamin* or neoplatin* or cismaplat* or CDDP).mp.	85282
20	(carboplatin or paraplatin*).mp.	19538
21	Tegafur/	5949
22	(tegafur or fl?orafur* or sunfural* or furflucil* or futraful* or lifril*).mp.	6611
23	Uracil/ or UFT*.mp.	11925
24	(atezolizumab or Tecentriq*).mp.	2332
25	(durvalumab or imfinzi*).mp.	1172
26	(cemiplimab or libtayo*).mp.	252
27	(avelumab or bavencio*).mp.	780
28	Nivolumab/	4432
29	(nivolumab or opdivo*).mp.	8248

30	(pembrolizumab or keytruda*).mp.	7409
31	(osimertinib or Tagrisso*).mp.	2063
32	Erlotinib Hydrochloride/	4277
33	(erlotinib or tarceva*).mp.	7653
34	Gefitinib/	4879
35	(gefitinib or iressa*).mp.	8164
36	Afatinib/	930
37	(afatinib or gi?otrif*).mp.	1881
38	Docetaxel/	11795
39	(docetaxel or taxotere*).mp.	18955
40	(gemcitabine or gemzar*).mp.	19536
41	Etoposide/	17440
42	(etoposide or Vepesid*).mp.	27214
43	Pemetrexed/	2420
44	(pemetrexed or Alimta*).mp.	4125
45	Vinorelbine/	2818
46	(vinorelbine or navelbine*).mp.	4396
47	(supportive care or BSC).mp.	21606
48	or/12-47	560842
49	"Health Care Economics and Organizations"/ or Economics/	27456
50	exp Cost-Benefit Analysis/	90096
51	Health Care Costs/	43336
52	exp "Fees and Charges"/	31154
53	Budgets/	11621
54	"Value of Life"/	5792
55	budget*.ti,ab.	33360
56	cost*.ti,ab.	717065
57	(economic* or pharmaco?economic*).ti.	56284
58	(price* or pricing*).ti,ab.	48253
59	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	190477
60	(financ* or fee or fees).ti,ab.	144708
61	(value adj2 (money or monetary)).ti,ab.	2798
62	or/49-61	977430
63	11 and 48 and 62	188
64	limit 63 to yr="2021 -Current"	27

EBM Reviews (Ovid): ACP Journal Club 1991 to June 2022, **Cochrane Central Register of Controlled Trials** May 2022**, Cochrane Database of Systematic Reviews** 2005 to June 29, 2022, **Cochrane Clinical Answers** June 2022
Accessed 4th July 2022

Table 64. EBM Reviews (Ovid): ACP Journal Club, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Review, Cochrane Clinical Answers, July 2022 update

#	Searches	Results
1	exp Carcinoma, Non-Small-Cell Lung/	4825
2	((lung* or pulmonary) adj2 (carcinom* neoplasm* or cancer* or tumo?r* or malignan*)).mp.	24467
3	non.mp.	273596
4	2 and 3	16540
5	NSCLC.mp.	10970
6	1 or 4 or 5	17490
7	(resectable or resected).mp.	9255
8	(early or early-stage or early stage).mp.	145769
9	("stage 0" or "stage 1" or "stage I" or "stage 2" or "stage II" or "stage 3*" or "stage III*").mp.	29903
10	or/7-9	177398
11	6 and 10	6429
12	Chemotherapy, Adjuvant/	4034
13	Neoadjuvant Therapy/	1434
14	Drug Therapy/ or Antibodies, Monoclonal/	6832
15	Radiotherapy/ or Radiotherapy, Adjuvant/ or Chemoradiotherapy, Adjuvant/	2380
16	surgical oncology/ or thoracic surgery/	180
17	Platinum/ or Carboplatin/ or Cisplatin/	7382
18	(platinum adj2 (chemo* or antineoplastic* or compound* or formulation*)).mp.	3773
19	(cisplatin or Cisplatinum or platamin* or neoplatin* or cismaplat* or CDDP).mp.	16298
20	(carboplatin or paraplatin*).mp.	8182
21	Tegafur/	623
22	(tegafur or fl?orafur* or sunfural* or furflucil* or futraful* or lifril*).mp.	1104
23	Uracil/ or UFT*.mp.	780
24	(atezolizumab or Tecentriq*).mp.	1178
25	(durvalumab or imfinzi*).mp.	859
26	(cemiplimab or libtayo*).mp.	70
27	(avelumab or bavencio*).mp.	338
28	Nivolumab/	592
29	(nivolumab or opdivo*).mp.	2504
30	(pembrolizumab or keytruda*).mp.	2437
31	(osimertinib or Tagrisso*).mp.	361

32	Erlotinib Hydrochloride/	568
33	(erlotinib or tarceva*).mp.	1883
34	Gefitinib/	326
35	(gefitinib or iressa*).mp.	1214
36	Afatinib/	71
37	(afatinib or gi?otrif*).mp.	478
38	Docetaxel/	2294
39	(docetaxel or taxotere*).mp.	8267
40	(gemcitabine or gemzar*).mp.	6783
41	Etoposide/	1845
42	(etoposide or Vepesid*).mp.	4594
43	Pemetrexed/	725
44	(pemetrexed or Alimta*).mp.	2414
45	Vinorelbine/	579
46	(vinorelbine or navelbine*).mp.	2036
47	(supportive care or BSC).mp.	5088
48	or/12-47	57791
49	"Health Care Economics and Organizations"/ or Economics/	48
50	exp Cost-Benefit Analysis/	7741
51	Health Care Costs/	2400
52	exp "Fees and Charges"/	254
53	Budgets/	30
54	"Value of Life"/	33
55	budget*.ti,ab.	1370
56	cost*.ti,ab.	78823
57	(economic* or pharmaco?economic*).ti.	4396
58	(price* or pricing*).ti,ab.	2805
59	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	32114
60	(financ* or fee or fees).ti,ab.	9307
61	(value adj2 (money or monetary)).ti,ab.	354
62	or/49-61	88538
63	11 and 48 and 62	121
64	limit 63 to yr="2021 -Current"	30

EconLit 1886 to June 23, 2022
Accessed 24th June 2022

Table 65. Econlit, July 2022 Update

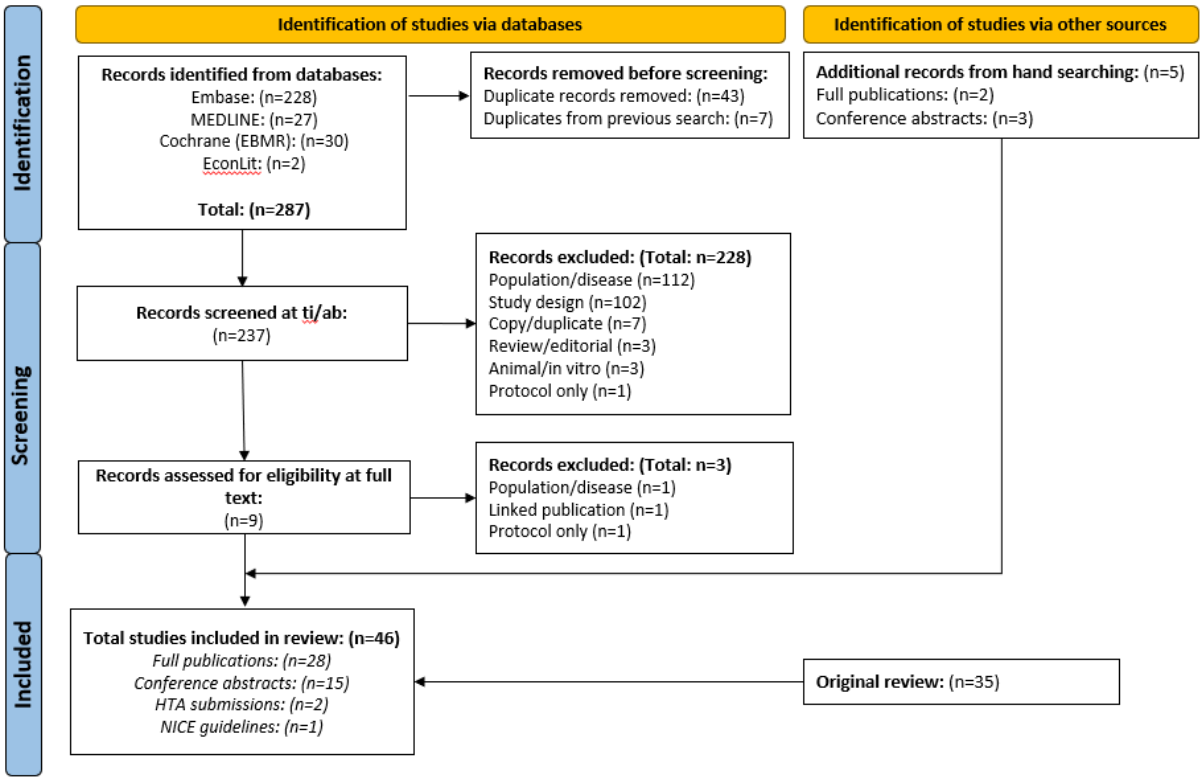
	Searches	Results
1	((lung* or pulmonary) adj2 (carcinom* neoplasm* or cancer* or tumo?r* or malignan*)).mp.	157
2	non.mp.	182474
3	1 and 2	45
4	limit 3 to yr="2021 -Current"	2

Overall summary

Across the original review (March 2021) and the July 2022 update, a total of 46 relevant economic evaluations were identified for inclusion (full publications, N=28; abstracts, N=15; NICE guidelines, N=1; HTA submissions, N=2).

The flow of studies through the review is summarised in the PRISMA flow diagram in Figure 33.

Figure 33. PRISMA flow diagram for economic evaluation SLR



Abbreviations: EBMR - Evidence based medicine reviews, NICE - National Institute for Health and Care Excellence, PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses, SLR - systematic literature review.

1.5.3 Description of identified studies: full publications

HRQoL data

A total of 22 unique cost utility analyses were identified by the current review (published economic evaluations, N=18 [34-51]; NG122 evidence reviews, N=2 [52]; HTA submissions, N=2 [53, 54]). Utility values were obtained from a range of sources, as detailed in Table 66. Rows shaded in green indicate sources of utilities that were identified and included in the HRQOL/HSUV SLR conducted concurrently with the current SLR; rows shaded in orange indicate sources of utilities that were not identified by the HRQOL/HSUV SLR (reasons for ineligibility are outlined in the comments column of the table). Note: in two studies the source of utility values was unclear/not reported and therefore they are not included in Table 66 [40, 42]. The most commonly cited published sources of utility values across the included studies were Doyle et al (2008) [55] and Nafees et al (2008) [56]; however, both of these studies

report utilities for health states associated with advanced/metastatic stages of NSCLC. This indicates a lack of suitable utility values specifically for patients with early-stage NSCLC for use in economic evaluations.

Table 66. Summary of sources of utility values

Source of data	Cited by	Comments
Original review		
Doyle et al (2008) [55]	Paix et al (2018) [45] Shah et al (2013) [47] Sher et al (2011) [48]	Focus on advanced NSCLC
Nafees et al (2008) [56]	NG122 (B & C) [52] Wolff et al (2021) [50]	Focus on advanced NSCLC
Bendixen et al (2016) [57]	Bendixen et al (2019) [34]	Two publications are linked; utility values only reported in Bendixen et al (2019) (included in HSUV SLR)
Chen et al (2002) [58]	Ferguson (2003) [41]	Focus on advanced NSCLC
Clegg et al (2001) [59]	Ferguson (2003) [41]	Review of clinical effectiveness and cost-effectiveness of various treatments in NSCLC
Clegg et al (2002) [60]	Ferguson (2003) [41]	Review; focus on advanced NSCLC
Coy et al (2000) [61]	Ferguson (2003) [41]	Focus on advanced NSCLC
Earle et al (1999) [62]	Ferguson (2003) [41]	Pre-2011 cost study
Evans et al (1997) [63]	Ferguson (2003) [41]	Pre-2011 cost study
Evans (2005) [64]	Louie et al (2014) [44]	Describes health state descriptors for Canadians – see also McIntosh et al (2007) [65]
Grutters et al (2010) [42]	Bongers et al (2015) [39] NG122 (C) [52] Ramaekers et al (2013) [46]	Included in current SLR of economic evaluations and HSUV SLR; does not report primary HSUVs but source of estimates is unclear (refers to a cross-sectional study but no reference provided)
Handy et al (2002) [66]	Ferguson (2003) [41]	Included as tagged HRQOL study
Lees et al (2002) [67]	Ferguson (2003) [41]	Focus on advanced NSCLC
Li et al (2002) [68]	Ferguson (2003) [41]	Included as tagged HRQOL study
Lester-Coll et al (2016a) [69]	NG122 (B) [52]	Focus on advanced NSCLC
Mahadevia et al (2003) [70]	Kent et al (2005) [43]	Non-relevant economic evaluation; lung cancer screening in smokers vs non-smokers
Mangione et al (1997) [71]	Ferguson (2003) [41]	Included as tagged HRQOL study
McIntosh et al (2007) [65]	Louie et al (2014) [44]	Study eliciting Canadian population preferences for various health states; see also Evans (2005) [64]

Source of data	Cited by	Comments
Rittmeyer et al (2017) [72]	Wolff et al (2021) [50]	Focus on advanced NSCLC
Sacristan et al (2000) [73]	Ferguson (2003) [41]	Focus on advanced NSCLC
Sturza (2010) [74]	Bongers et al (2015) [39]	Review of utility values in lung cancer
Tramontano et al (2015) [21]	NG122 (C) [52]	Included in HSUV SLR
Trippoli et al (2001) [22]	van Loon et al (2010) [49]	Included in HSUV SLR
Wolff et al (2018) [75]	Wolff et al (2020) [51] Wolff et al (2021) [50]	Included in HSUV SLR
Yang et al (2014) [27]	NG122 (C) [52]	Included in HSUV SLR
Zieren et al (1996) [76]	Ferguson (2003) [41]	Included as tagged HRQOL study
July 2022 update		
ADAURA trial (internal report)	NICE (2022) [54] CADTH (2022) [53]	Internal report
Bendixen et al (2016) [57]	Heiden et al (2022) [35]	Linked to Bendixen 2019 (included in the HSUV SLR)
Bodnar et al (2016) [77]	Lemmon et al (2022) [38]	Abstract publication linked to full publications of the ADAURA trial already included in the HSUV SLR
Chouaid et al (2013) [78]	Lemmon et al (2022) [38]	Focus on advanced NSCLC
FLAURA trial (internal report)	NICE (2022) [54]	Internal report focused on locally advanced and metastatic NSCLC
Huang et al (2019) [79]	Heiden et al (2022) [35]	Focus on advanced NSCLC
Jiang et al (2019) [80]	CADTH (2022) [53] Lemmon et al (2022) [38]	Focus on advanced NSCLC
Labbe et al (2017) [81]	NICE (2022) [54]	Focus on patients with metastatic lung cancer
Lester-Coll et al (2016b) [82]	Lemmon et al (2022) [38]	Non-relevant economic evaluation; focus on patients with brain metastases
Lester-Coll et al (2016c) [83]	Lemmon et al (2022) [38]	Non-relevant economic evaluation; focus on patients with brain metastases
Nafees et al (2017) [84]	CADTH (2022) [53] Lemmon et al (2022) [38]	Focus on metastatic NSCLC
NICE (2020) [85]	CADTH (2022) [53]	Focus on advanced NSCLC
Soria et al (2017) [86]	CADTH (2022) [53]	Focus on advanced NSCLC

Source of data	Cited by	Comments
Torrance et al (1996) [87]	Heiden et al (2022) [35]	Unrelated to NSCLC; participants were a random sample of the general population
Yang et al (2014) [88]	Lemmon et al (2022) [38]	Included in HSUV SLR

Abbreviations: CADTH - Canadian Agency for Drugs and Technologies in Health, HRQOL - health-related quality of life, HSUV - health state utility value, NICE - National Institute for Health and Care Excellence, NSCLC - non-small cell lung cancer, SLR - systematic literature review

1.5.4 Quality assessment and generalisability of estimates

As a part of the evidence generation to inform inputs in the health economic model a global SLR was performed assessing economic evaluations within the disease area of NSCLC. Assessment of economic evaluations was undertaken using the criteria of the NICE single technology appraisal (STA) specification for manufacturer submission of evidence (June 2012), as adapted from Drummond and Jefferson (1996). The key criteria for assessing the relevance and quality of economic evaluations were:

- relevance to study question
- details of important biases in the data used
- was cost-effectiveness estimated using the correct methods?

Quality assessment of the published economic evaluations presented as full publications revealed that in general, the identified studies had well defined objectives, treatments, and populations, and clearly reported methodologies. However, key modelling decisions (e.g. choice of model, choice of discount rate, choice of variables for sensitivity analysis) were often not justified. Further, while results were generally clearly reported, there was variability in the extent to which individual study caveats were discussed and issues relating to the generalisability of results were not consistently addressed. Commonly reported study limitations included: model simplifications and use of multiple assumptions (N=11) [35, 37, 38, 43, 46-50, 52, 89]; limited data availability/inherent limitations of model inputs (including absence of relevant utility values for early-stage NSCLC) (N=11) [35, 37, 38, 42, 45-48, 53, 90, 91]; limited generalisability of results (e.g., due to use of country-specific data inputs) (N=8) [36, 38-40, 45, 47, 48, 51]; lack of consideration of evolution of disease management and/or advances in treatment options over time (N=6) [40, 50-52, 90, 92]; reliance on retrospective and/or non-randomised studies for clinical model inputs (N=5) [51, 52, 91, 93, 94]; lack of consideration of indirect costs (i.e., use of payer rather than societal perspective) (N=7) [36-38, 46, 48, 53, 92]; and potential unobserved confounding bias (N=3) [91, 92, 95].

Utility values identified in the global economic evaluation SLR were used to inform utility values in the health state of recurrences. No additional Danish studies including HRQoL data were identified within the global SLR. The identified studies including HRQoL data were assessed in the same manner as described in section 1.4. The generalisability is limited, due to lack of IPD and thereby mapping to Danish EQ-5D-5L and tariffs. However, this is the only option that allows consequent choice of EQ-5D questionnaire and tariffs to ensure validity throughout the included evidence.

1.6 Unpublished data

No unpublished data was used.

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Appendix I Mapping of HRQoL data

Not applicable. No mapping has been conducted.

Appendix J Probabilistic sensitivity analyses

All model parameters used to inform the probabilistic sensitivity analysis (PSA) are found in the "*Parameters*" sheet in the model. All parameters included in the PSA, their numerical values, lower- and upper CE value, distribution type and standard error are presented in Table 67.

Table 67: List of model parameter values included in the probabilistic sensitivity analysis

Input sheet	Parameter	Mean	α	β	Distribution	SE
Efficacy Inputs						
Cured Patients						
	Maximum proportion of cured patients	91,50%			Beta	0,09
	Cure proportion starts to increase (month)	24,00			Normal	2,40
	Cure proportion maximum reached (month)	60,00			Normal	6,00
Locoregional Recurrence						
Treatment Setting						
	% of Patients by Treatment Intent - Curative Treatment	95%			Dirichlet	0,10
	% of Patients by Treatment Intent - Palliative Treatment	5%			Dirichlet	0,01
	% of Patients by Treatment Intent - No Treatment	0%			Dirichlet	0,00
Efficacy by Treatment Intent						

	Transition Probability to Metastatic Recurrence (1L) - Curative Treatment - Treatment option - Digitised Data	3,996			Normal	0,28
	Transition Probability to Metastatic Recurrence (1L) - Curative Treatment - Treatment option - Simple Calculation	4%	96,315	2543,81	Beta	0,00
	% Progression as first event	77%	22,230	6,64	Beta	0,08
	Transition Probability to Death - Palliative Treatment and No Treatment - Treatment Option - Digitised Data	2,54			Normal	0,18
	Transition Probability to Death - Palliative Treatment and No Treatment - Treatment Option - Simple Calculation	14%	86,27	548,50	Beta	0,01
Metastatic Recurrence (1L)						
Efficacy by Treatment Intent						
	% of Patients by Treatment Intent - Treatment	75%	24,25	8,08	Beta	0,08
	Treatment Market Shares - Atezolizumab Arm - Treatment Option 1	75%			Dirichlet	0,08
	Treatment Market Shares - Atezolizumab Arm - Treatment Option 2	25%			Dirichlet	0,03
	Treatment Market Shares - Atezolizumab Arm - Treatment Option 3	0%			Dirichlet	0,00
	Treatment Market Shares - Atezolizumab Arm - Treatment Option 4	0%			Dirichlet	0,00
	Treatment Market Shares - Best Supportive Care Arm - Treatment Option 1	75%			Dirichlet	0,08

	Treatment Market Shares - Best Supportive Care Arm - Treatment Option 2	25%			Dirichlet	0,03
	Treatment Market Shares - Best Supportive Care Arm - Treatment Option 3	0%			Dirichlet	0,00
	Treatment Market Shares - Best Supportive Care Arm - Treatment Option 4	0%			Dirichlet	0,00
	Transition Probability to Metastatic Recurrence (2L) - Treatment - Immunotherapy	2,86			Normal	0,11
	Transition Probability to Metastatic Recurrence (2L) - Treatment - Chemotherapy	2,09			Normal	0,11
	% Progression as first event	79%	20,21	5,37	Beta	0,08
	Transition Probability to Death - No Treatment - Digitised Data	2,21			Normal	0,06
	Transition Probability to Death - No Treatment - Simple Calculation	23%	76,66	255,14	Beta	0,02
Metastatic Recurrence (2L)						
Efficacy by Treatment Intent						
	% of Patients by Treatment Intent - Treatment	45%	54,55	66,67	Beta	0,05
	Treatment Market Shares - Atezolizumab Arm - Treatment Option 1	0%			Dirichlet	0,00
	Treatment Market Shares - Atezolizumab Arm - Treatment Option 2	100%			Dirichlet	0,10
	Treatment Market Shares - Atezolizumab Arm - Treatment Option 3	0%			Dirichlet	0,00

	Treatment Market Shares - Atezolizumab Arm - Treatment Option 4	0%			Dirichlet	0,00
	Treatment Market Shares - Best Supportive Care Arm - Treatment Option 1	0%			Dirichlet	0,00
	Treatment Market Shares - Best Supportive Care Arm - Treatment Option 2	100%			Dirichlet	0,10
	Treatment Market Shares - Best Supportive Care Arm - Treatment Option 3	0%			Dirichlet	0,00
	Treatment Market Shares - Best Supportive Care Arm - Treatment Option 4	0%			Dirichlet	0,00
	Transition Probability to Death - Treatment - Immunotherapy	4,45			Normal	0,06
	Transition Probability to Death - Treatment - Chemotherapy	4,15			Normal	0,06
	Transition Probability to Death - No Treatment - Digitised Data	2,21			Normal	0,06
	Transition Probability to Death - No Treatment - Simple Calculation	23%	76,66	255,14	Beta	0,02
Cost Inputs						
Disease Free Survival						
Other Healthcare Resource Use						
	Chest Radiography	4	100	0,04	Gamma	0,4
	Electrocardiogram	0			Gamma	0
	Outpatient Visit	17	100	0,17	Gamma	1,7

	Community Nurse Visit	0			Gamma	0
	Clinical Nurse Specialist	0			Gamma	0
	Bronchoscopy	0			Gamma	0
	Thoracoscopy	0			Gamma	0
	Blood samples	17			Gamma	1,7
	Placeholder	0			Gamma	0
	Placeholder	0			Gamma	0
Adverse Event Management						
	Alanine aminotransferase increased	0,00%	0	104	Beta	
	Aspartate aminotransferase increased	0,00%	0	104	Beta	
	Asthenia	0,96%	1	104	Beta	
	Axonal neuropathy	0,00%	0	104	Beta	
	Colitis	0,96%	1	104	Beta	
	Demyelinating polyneuropathy	0,96%	1	104	Beta	
	Diarrhoea	0,00%	0	104	Beta	
	Drug eruption	0,00%	0	104	Beta	
	Drug-induced liver injury	0,96%	1	104	Beta	
	Dyspepsia	0,00%	0	104	Beta	
	Encephalitis	0,96%	1	104	Beta	
	Gait disturbance	0,00%	0	104	Beta	
	Gastritis	0,00%	0	104	Beta	

	Genital rash	0,96%	1	104	Beta	
	Hepatic function abnormal	1,92%	2	104	Beta	
	Hyperglycaemia	0,00%	0	104	Beta	
	Hypersensitivity	0,96%	1	104	Beta	
	Hyponatraemia	0,00%	0	104	Beta	
	Immune-mediated adverse reaction	0,00%	0	104	Beta	
	Inappropriate antidiuretic hormone secretion	0,96%	1	104	Beta	
	Interstitial lung disease	0,96%	1	104	Beta	
	Leukopenia	0,96%	1	104	Beta	
	Meningitis	0,96%	1	104	Beta	
	Multiple organ dysfunction syndrome	0,00%	0	104	Beta	
	Myalgia	0,00%	0	104	Beta	
	Myocarditis	0,00%	0	104	Beta	
	Neuropathy peripheral	0,00%	0	104	Beta	
	Neutropenia	0,96%	1	104	Beta	
	Parapsoriasis	0,96%	1	104	Beta	
	Platelet count decreased	0,00%	0	104	Beta	
	Pneumonia	0,00%	0	104	Beta	
	Pneumonitis	0,96%	1	104	Beta	
	Pyrexia	0,96%	1	104	Beta	
	Rash	0,96%	1	104	Beta	

	Rash maculo-papular	0,00%	0	104	Beta	
	Sarcoidosis	0,96%	1	104	Beta	
	Secondary adrenocortical insufficiency	0,00%	0	104	Beta	
	Septic shock	0,00%	0	104	Beta	
	Thrombocytopenia	0,96%	1	104	Beta	
	Vomiting	0,00%	0	104	Beta	
Locoregional Recurrence						
Curative Treatment						
	Adverse Event Cost - Cost (monthly)	0			Gamma	0
	Chest Radiography	4	100	0,04	Gamma	0,4
	Electrocardiogram	0			Gamma	0
	Outpatient Visit	17	100	0,17	Gamma	1,7
	Community Nurse Visit	0			Gamma	0
	Clinical Nurse Specialist	0			Gamma	0
	Bronchoscopy	0			Gamma	0
	Thoracoscopy	0			Gamma	0
	Blood samples	17	100	0,17	Gamma	1,7
	Placeholder	0			Gamma	0
	Placeholder	0			Gamma	0
Palliative Treatment						
	Adverse Event Cost - Cost (monthly)	0			Gamma	0

	Chest Radiography	4	100	0,04	Gamma	0,4
	Electrocardiogram	0			Gamma	0
	Outpatient Visit	17	100	0,17	Gamma	1,7
	Community Nurse Visit	0			Gamma	0
	Clinical Nurse Specialist	0			Gamma	0
	Bronchoscopy	0			Gamma	0
	Thoracoscopy	0			Gamma	0
	Blood samples	17	100	0,17	Gamma	1,7
	Placeholder	0			Gamma	0
	Placeholder	0			Gamma	0
Metastatic Recurrence (1L)						
Treatment Regimens						
	Adverse Event Management Costs - Treatment 1	487,22 DKK	100	4,872	Gamma	48,72
	Adverse Event Management Costs - Treatment 2	434,22 DKK	100	4,342	Gamma	43,42
	Adverse Event Management Costs - Treatment 3	434,22 DKK	100	4,342	Gamma	43,42
	Adverse Event Management Costs - Treatment 4	487,22 DKK	100	4,872	Gamma	48,72
Follow-Up Costs						
	Chest Radiography	4	100	0,04	Gamma	0,4

	Electrocardiogram	0			Gamma	0
	Outpatient Visit	17	100	0,17	Gamma	1,7
	Community Nurse Visit	0			Gamma	0
	Clinical Nurse Specialist	0			Gamma	0
	Bronchoscopy	0			Gamma	0
	Thoracoscopy	0			Gamma	0
	Blood samples	17	100	0,17	Gamma	1,7
	Placeholder	0			Gamma	0
	Placeholder	0			Gamma	0
No Treatment - Other Healthcare Resource Use						
	Chest Radiography	4	100	0,04	Gamma	0,4
	Electrocardiogram	0			Gamma	0
	Outpatient Visit	17	100	0,17	Gamma	1,7
	Community Nurse Visit	0			Gamma	0
	Clinical Nurse Specialist	0			Gamma	0
	Bronchoscopy	0			Gamma	0
	Thoracoscopy	0			Gamma	0
	Blood samples	17	100	0,17	Gamma	1,7
	Placeholder	0			Gamma	0
	Placeholder	0			Gamma	0

Metastatic Recurrence (2L)						
Metastatic Recurrence (2L)						
	Adverse Event Management Costs - Treatment 1	17,44 DKK	100	1,74	Gamma	22,43
	Adverse Event Management Costs - Treatment 2	17,44 DKK	100	1,74	Gamma	17,08
	Adverse Event Management Costs - Treatment 3	2.106,07 DKK	100	210,61	Gamma	1831,18
	Adverse Event Management Costs - Treatment 4	17,44 DKK	100	1,74	Gamma	15,28
Follow-Up Care						
	Chest Radiography	4	100	0,04	Gamma	0,4
	Electrocardiogram	0			Gamma	0
	Outpatient Visit	17	100	0,17	Gamma	1,7
	Community Nurse Visit	0			Gamma	0
	Clinical Nurse Specialist	0			Gamma	0
	Bronchoscopy	0			Gamma	0
	Thoracoscopy	0			Gamma	0
	Blood samples	17	100	0,17	Gamma	1,7
	Placeholder	0			Gamma	0
	Placeholder	0			Gamma	0
No Treatment - Other Healthcare Resource Use						

	Chest Radiography	4	100	0,04	Gamma	0,4
	Electrocardiogram	0			Gamma	0
	Outpatient Visit	17	100	0,17	Gamma	1,7
	Community Nurse Visit	0			Gamma	0
	Clinical Nurse Specialist	0			Gamma	0
	Bronchoscopy	0			Gamma	0
	Thoracoscopy	0			Gamma	0
	Blood samples	17	100	0,17	Gamma	1,7
	Placeholder	0			Gamma	0
	Placeholder	0			Gamma	0
End of Life Cost						
	Type of Death - Natural death	0			Gamma	0
	Type of Death - Disease death	0			Gamma	0
Patient costs						
	Patient cost per hour	181,00 DKK	100	1,81	Gamma	18,10
	Patient cost treatment initiation (per cycle) ATZ	1.212,70 DKK	100	12,13	Gamma	121,27
	Patient cost treatment followed administration (per cycle) ATZ	663,37 DKK	100	6,63	Gamma	66,34
	Patient cost treatment initiation (per cycle) pembrolizumab	1.393,70 DKK	100	13,94	Gamma	139,37
	Patient cost treatment followed administration (per cycle) pembrolizumab	557,48 DKK	100	5,57	Gamma	55,75

	Patient cost treatment followed administration (per cycle) cisplatin	1.190,98 DKK	100	11,91	Gamma	119,10
	Patient cost treatment followed administration (per cycle) vinorelbine	30,77 DKK	100	0,31	Gamma	3,08
	Patient cost treatment followed administration (per cycle) docetaxel	647,98 DKK	100	6,48	Gamma	64,80
	Patient cost treatment followed administration (per cycle) No treatment	421,73 DKK	100	4,22	Gamma	42,17
Transportation costs						
	Cost per transportation (roundtrip)	140,00 DKK	100	1,40	Gamma	14,00
	Transportation cost per cycle first cycle	560,00 DKK	100	5,60	Gamma	56,00
	Transportation cost per cycle following cycles	405,83 DKK	100	4,06	Gamma	40,58
	Transportation cost per cycle patients off treatment	202,92 DKK	100	2,03	Gamma	20,29
Utility Inputs						
Disease Free Survival						
	Alanine aminotransferase increased	0			Beta	0
	Aspartate aminotransferase increased	0			Beta	0
	Asthenia	0			Beta	0
	Axonal neuropathy	0			Beta	0
	Colitis	0			Beta	0
	Demyelinating polyneuropathy	0			Beta	0

	Diarrhoea	0			Beta	0
	Drug eruption	0			Beta	0
	Drug-induced liver injury	0			Beta	0
	Dyspepsia	0			Beta	0
	Encephalitis	0			Beta	0
	Gait disturbance	0			Beta	0
	Gastritis	0			Beta	0
	Genital rash	0			Beta	0
	Hepatic function abnormal	0			Beta	0
	Hyperglycaemia	0			Beta	0
	Hypersensitivity	0			Beta	0
	Hyponatraemia	0			Beta	0
	Immune-mediated adverse reaction	0			Beta	0
	Inappropriate antidiuretic hormone secretion	0			Beta	0
	Interstitial lung disease	0			Beta	0
	Leukopenia	0			Beta	0
	Meningitis	0			Beta	0
	Multiple organ dysfunction syndrome	0			Beta	0
	Myalgia	0			Beta	0
	Myocarditis	0			Beta	0
	Neuropathy peripheral	0			Beta	0

	Neutropenia	0			Beta	0
	Parapsoriasis	0			Beta	0
	Platelet count decreased	0			Beta	0
	Pneumonia	0			Beta	0
	Pneumonitis	0			Beta	0
	Pyrexia	0			Beta	0
	Rash	0			Beta	0
	Rash maculo-papular	0			Beta	0
	Sarcoidosis	0			Beta	0
	Secondary adrenocortical insufficiency	0			Beta	0
	Septic shock	0			Beta	0
	Thrombocytopenia	0			Beta	0
	Vomiting	0			Beta	0

Abbreviations: 1L – first-line; 2L – second-line; DKK - Danish Krones; SE – standard error.

Appendix K ICER Convergence testing

Appendix L Supplementary data

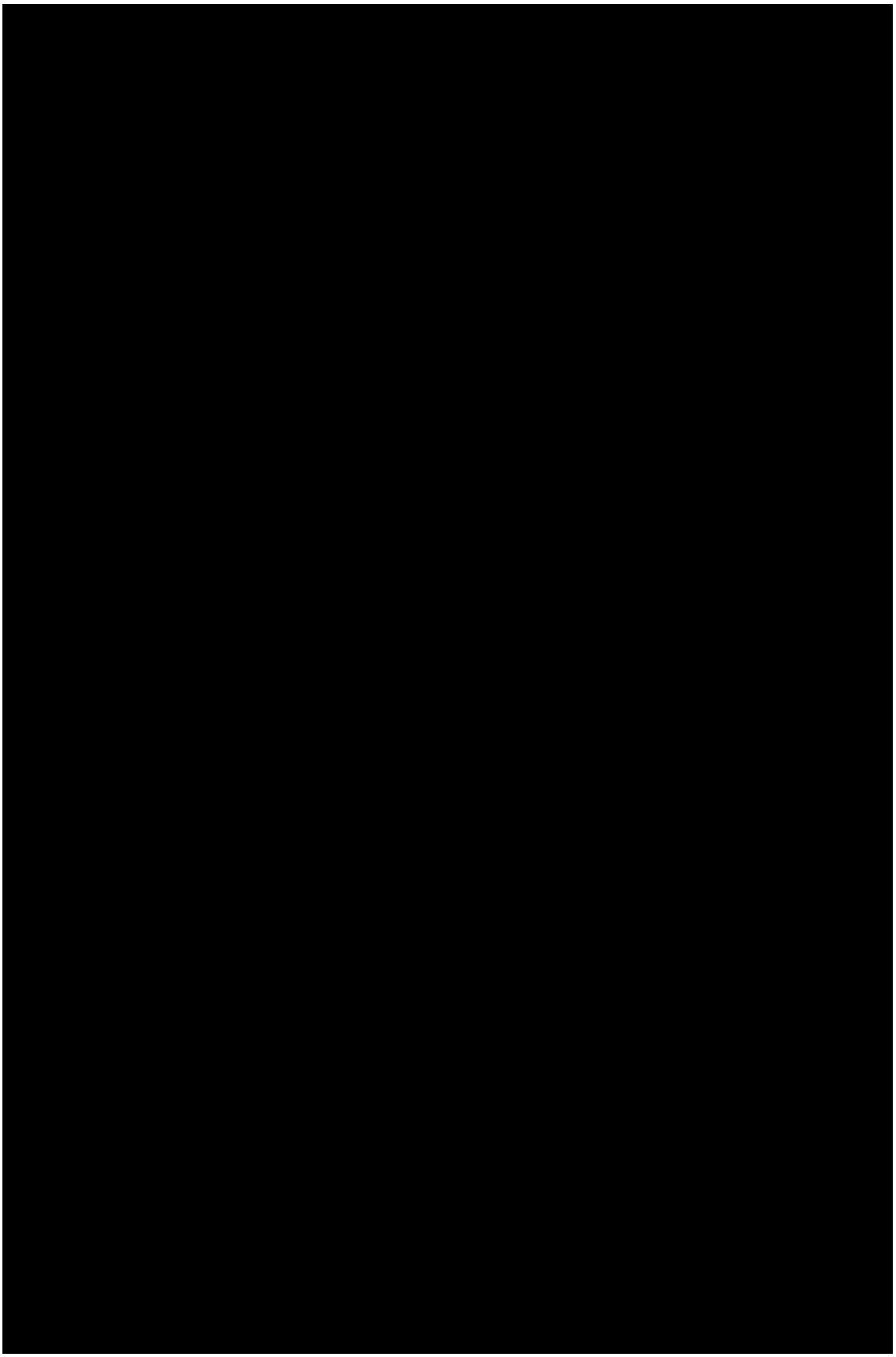
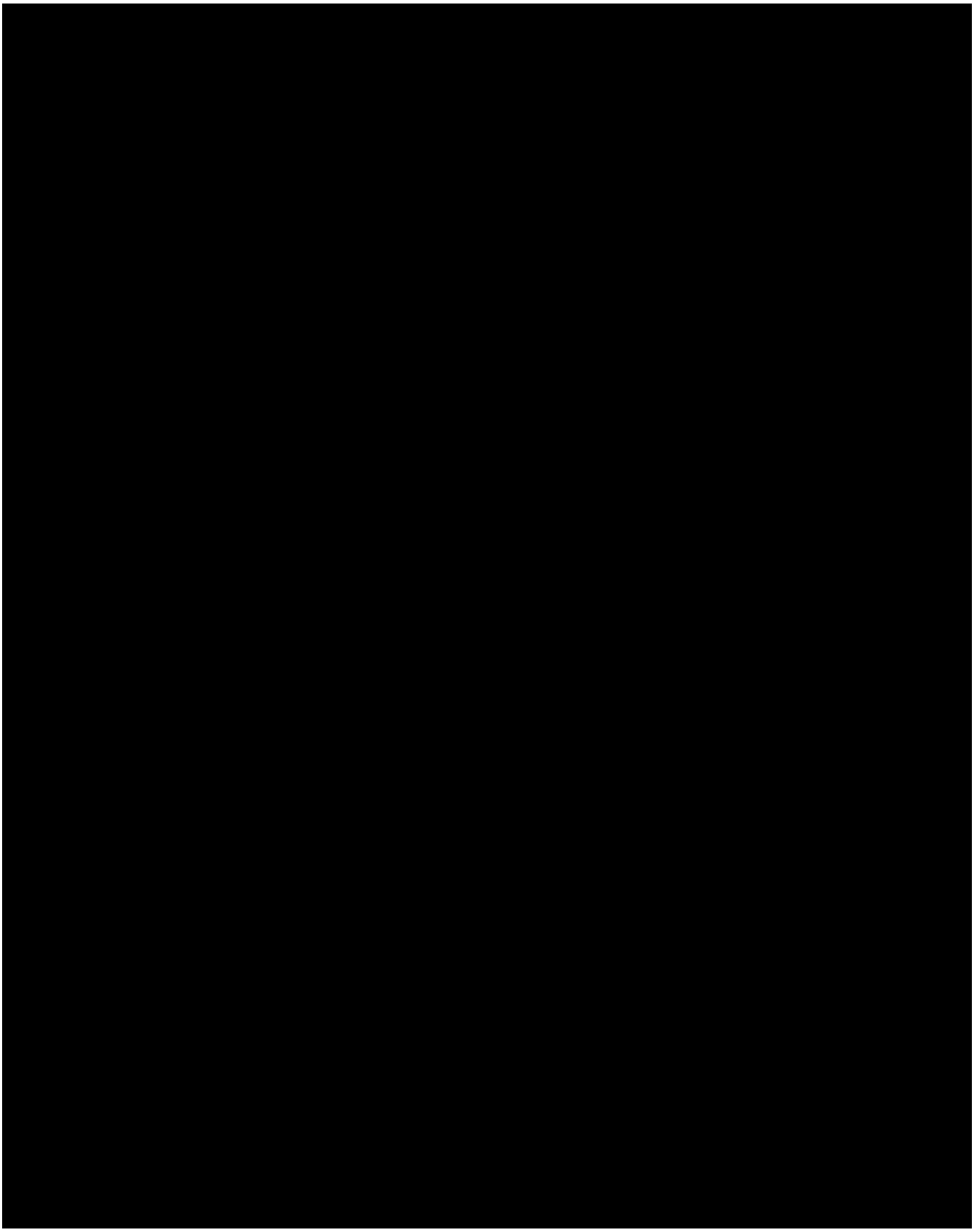
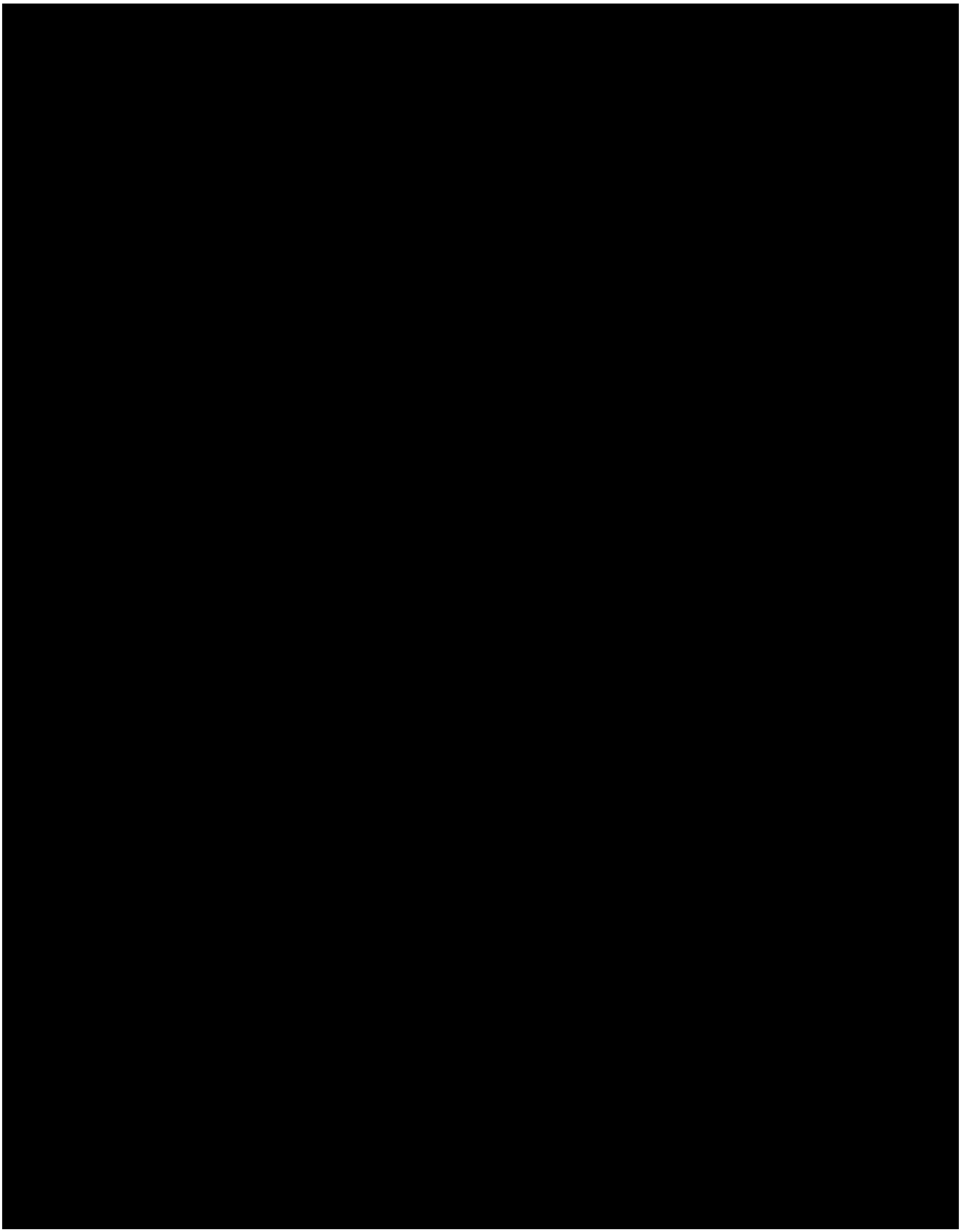
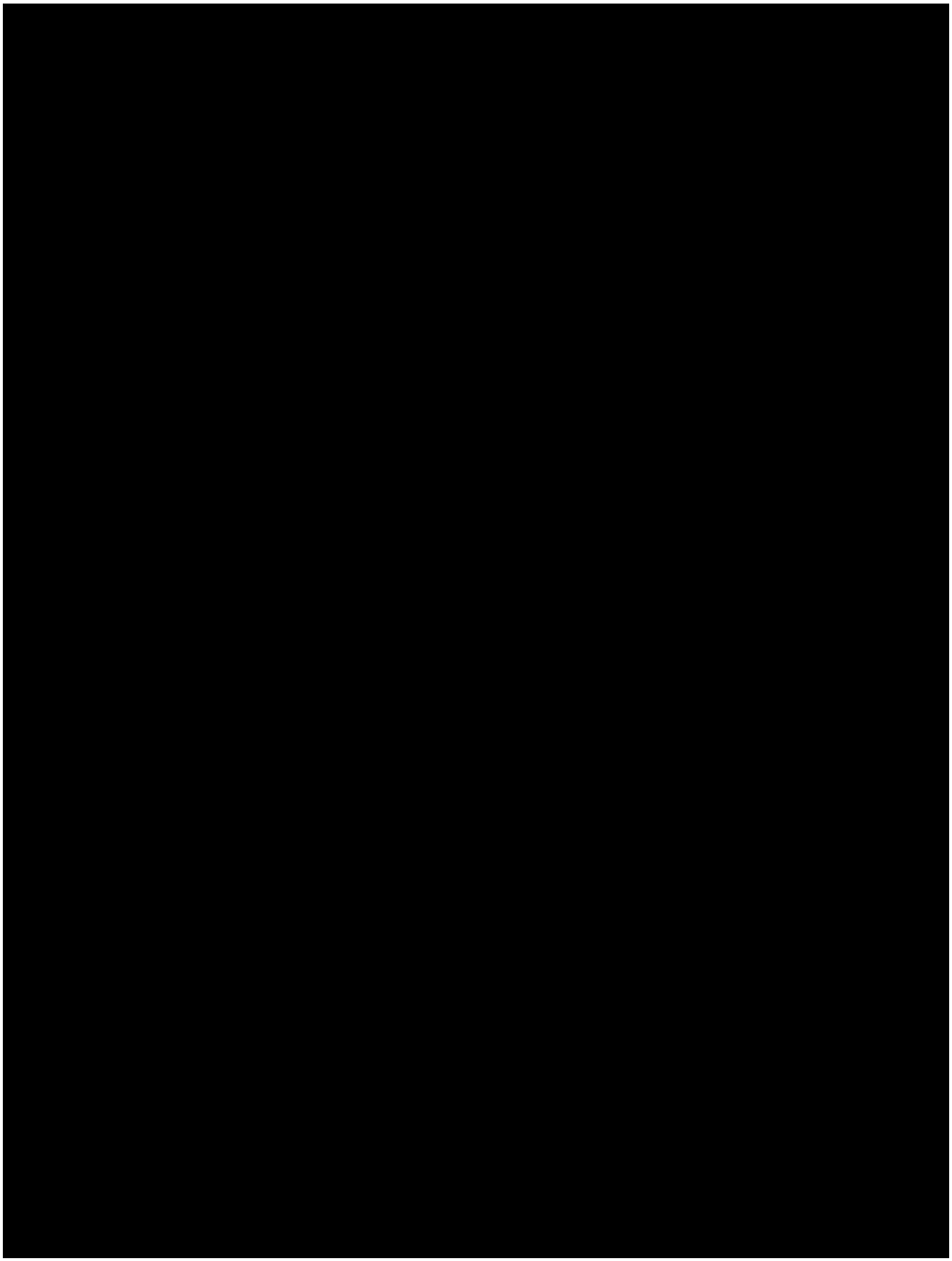


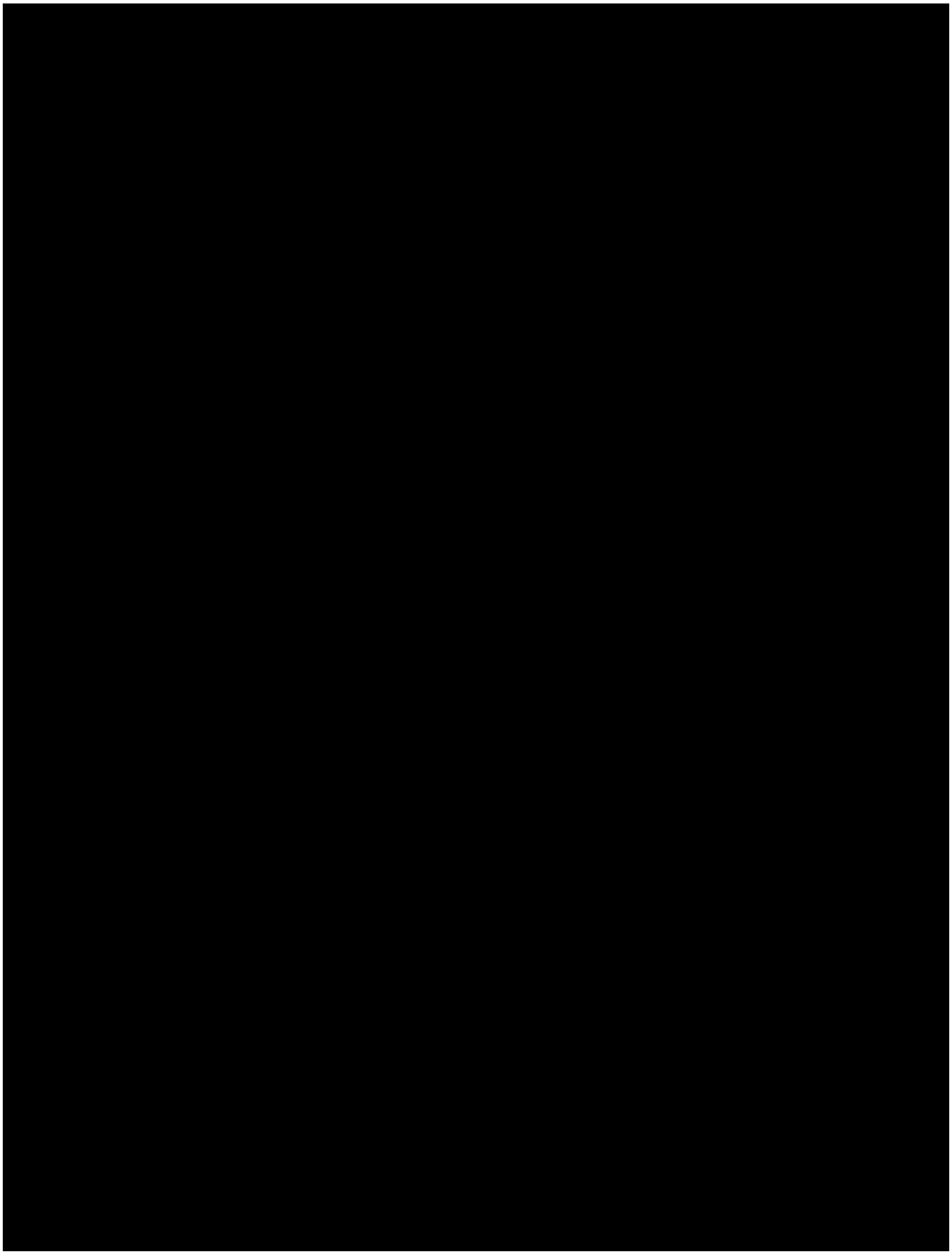
Figure 35: Patient populations characterised using the AJCC TNM 7th and 8th editions in the context of the IMpower010 trial.

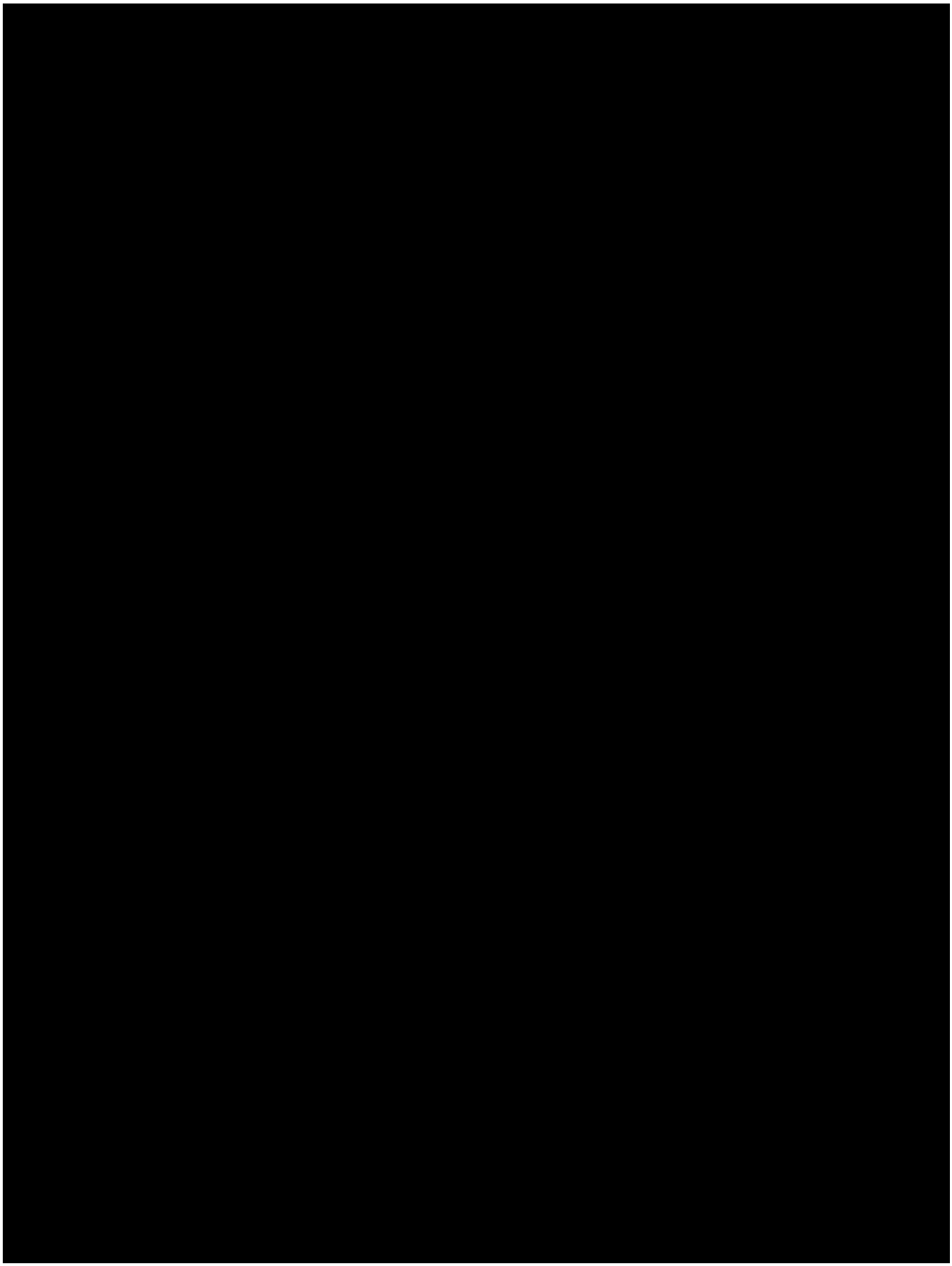
*Chest wall (including the parietal pleura and superior sulcus tumours), phrenic nerve, parietal pericardium ‡Mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, and carina. Abbreviations: cm – centimetre; DFS – disease-free survival. Figure is based on information from Felip et al. [19] and Goldstraw et al. [9].

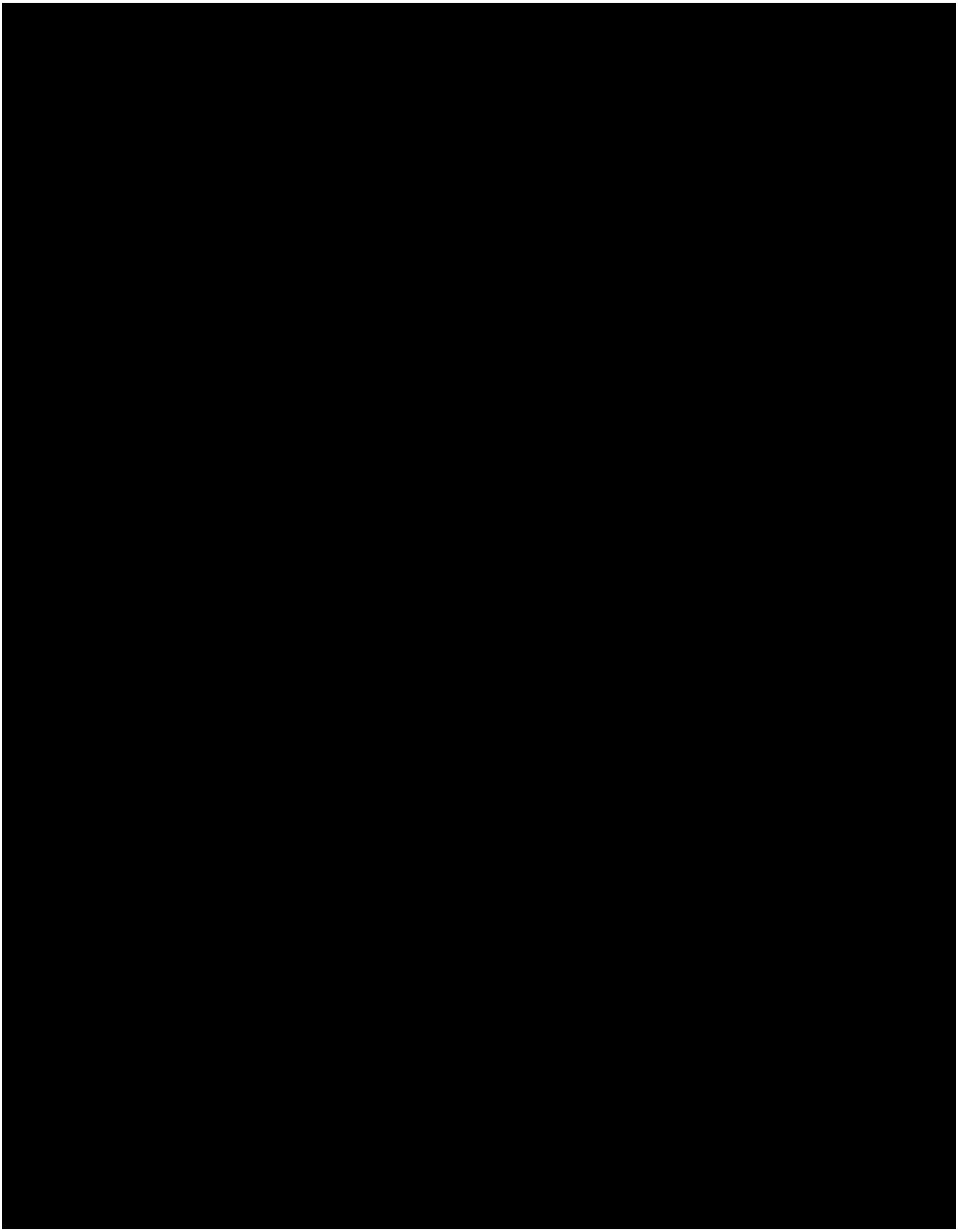












[redacted]

Data for PD-L1 ≥50% stage II–IIIA population (incl. EGFR/ALK+)

Disease-free survival

At data cut-off, the median duration of follow-up for the DFS analysis was 34.2 months in the PD-L1 ≥50% stage II-IIIA population. At this time, 28 (24.3%) of 115 patients in the atezolizumab arm and 52 (45.6%) of 114 in the BSC arm had experienced disease recurrence or death; the unstratified HR was 0.43 (95% CI, 0.27 to 0.68; p=0.0002) [19,27,32] (the stratified HR was 0.47 (95% CI, 0.29 to 0.75; p=0.0012) [27]). The median DFS could not be estimated for the atezolizumab arm (NE (95% CI, 42.3-NE) and was 35.7 months (95% CI, 29.7 to NE) in the BSC arm per Kaplan-Meier analysis [19,27].

A significantly higher proportion of patients remained disease-free at 3 years in the atezolizumab arm (73.8%; 95% CI, 64.4 to 83.2) than in the BSC-treated arm (48.6%; 95% CI, 38.0 to 59.2) with a difference in rate of 25.2% (95% CI, 11.0 to 39.4) (p=0.0005) [27]. The disease-free rate at 5 years could not be estimated in either arm [27].

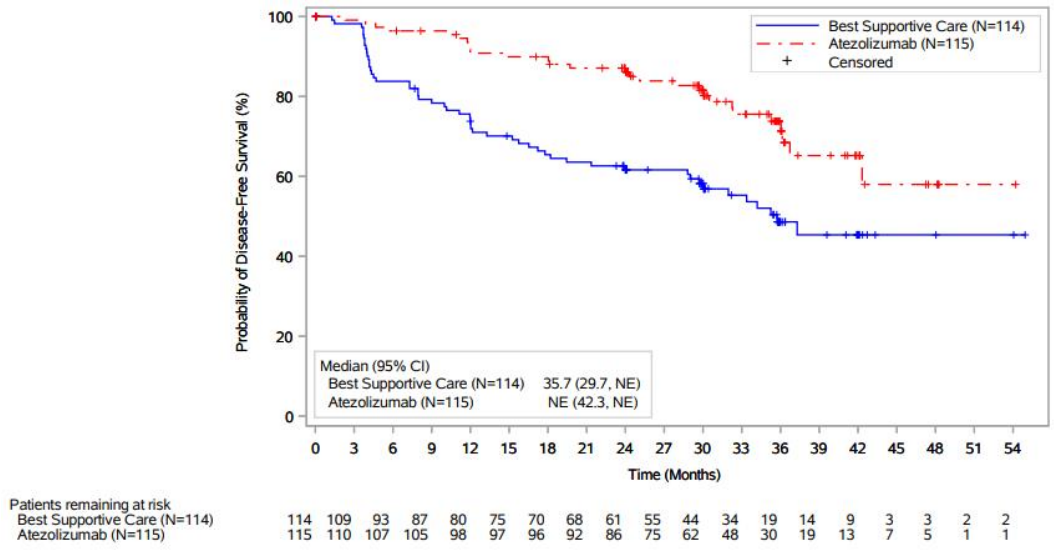


Figure 37: Kaplan-Meier estimate of DFS in the PD-L1 SP263 TC ≥50% stage II–IIIA population

Clinical data cutoff: 21 January 2021. Abbreviations: CI - confidence interval; DFS - disease-free survival; N - number of patients; NE - not evaluable; PD-L1 - programmed death-ligand 1; TC - tumour cell. Figure available in EMA's assessment report [27].

Table 70: DFS in the PD-L1 SP263 TC ≥50% stage II-IIIA population

Trial name	Intervention	Median follow-up	N	DFS			
				Median. mo (95% CI)	HR (95% CI)	DFS at 3 years, % (95% CI)	DFS at 5 years, % (95% CI)
IMpower010 [19,27]	ATZ	34.2 months	115	NE (42.3-NE)	0.43 (0.27-0.68)	73.8 (64.4-83.2)	NE (NE-NE)
	BSC		114	35.7 (29.7-NE)		48.6 (38.0-59.2)	NE (NE-NE)

Abbreviations: ATZ - atezolizumab; BSC - best supportive care; CI - confidence interval; DFS - disease-free survival; HR - hazard ratio; mo - months; N - number of patients; NE - not evaluable; PD-L1 - programmed death-ligand 1; TC - tumour cells.

Overall survival

At the time of the first data cutoff, an OS benefit was observed in the atezolizumab arm compared to the BSC arm; the unstratified HR was 0.37 (95% CI, 0.18 to 0.74; p=0.0036)) [27] (the stratified HR was 0.40 (95% CI, 0.20 to 0.81, p=0.0089) [27]).

A higher proportion of patients were alive at 3 years in the atezolizumab arm (90.9%; 95% CI, 85.2 to 96.7) compared to the BSC arm (76.7%; 95% CI, 68.4 to 85.0) with a difference in rate of 14.3% (95% CI, 4.2 to 24.4; p=0.0055). The OS rate at 5 years could not be estimated in either arm [27].

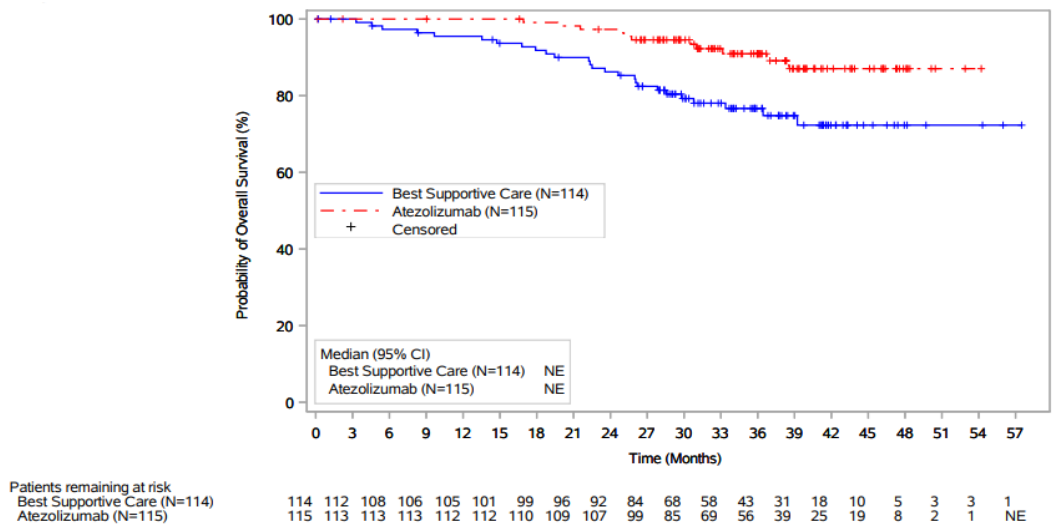


Figure 38: Kaplan-Meier estimate of OS in the PD-L1 SP263 TC ≥50% stage II–IIIA population

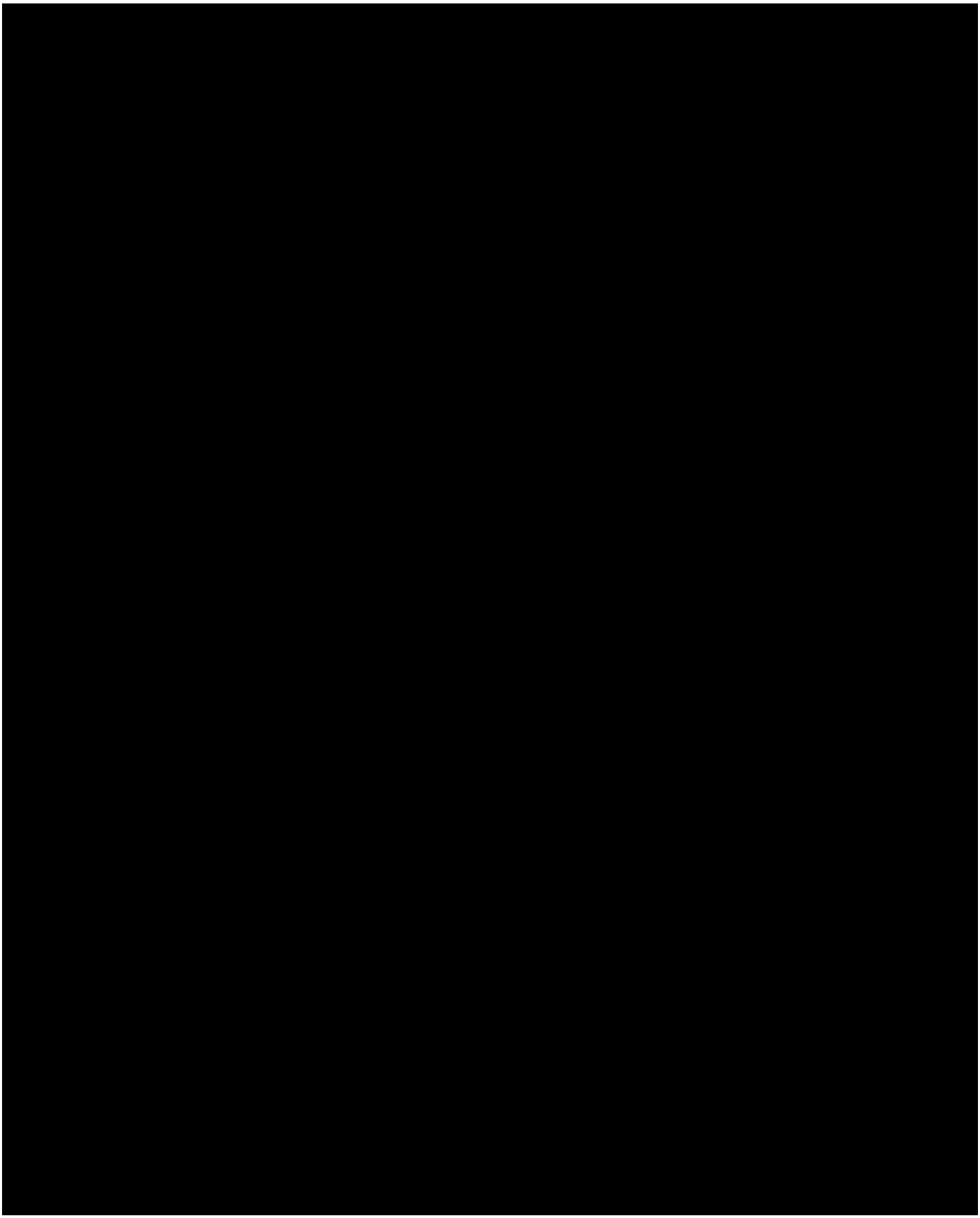
Clinical data cutoff: 21 January 2021. Abbreviations: CI - confidence interval; NE - not evaluable; OS - overall survival; PD-L1 - programmed death-ligand 1; TC - tumour cell. Figure available in EMA's assessment report [27].

At the time of the first prespecified interim analysis for OS (CCOD April 18, 2022), the unstratified HR for OS was 0.43 (95% CI, 0.24 to 0.78) in favour of atezolizumab over BSC [31]. Due to the low rate of death in both study arms, a median OS could not be estimated via Kaplan-Meier analysis [28].

Table 71: OS in the PD-L1 SP263 TC ≥50% stage II-IIIA population

Trial name	Intervention	Median follow-up	N	OS			
				Median. mo (95% CI)	HR (95% CI)	OS at 3 years, % (95% CI)	OS at 5 years, % (95% CI)
IMpower010 [27]	ATZ	34.2 months	115	NE (NE-NE)	0.37 (0.18-0.74)	90.9 (85.2-96.7)	NE (NE-NE)
	BSC		114	NE (NE-NE)		76.7 (68.4-85.0)	NE (NE-NE)

Abbreviations: ATZ - atezolizumab; BSC - best supportive care; CI - confidence interval; HR - hazard ratio; mo - months; N - number of patients; NE - not evaluable; OS - overall survival; PD-L1 - programmed death-ligand 1; TC - tumour cells.



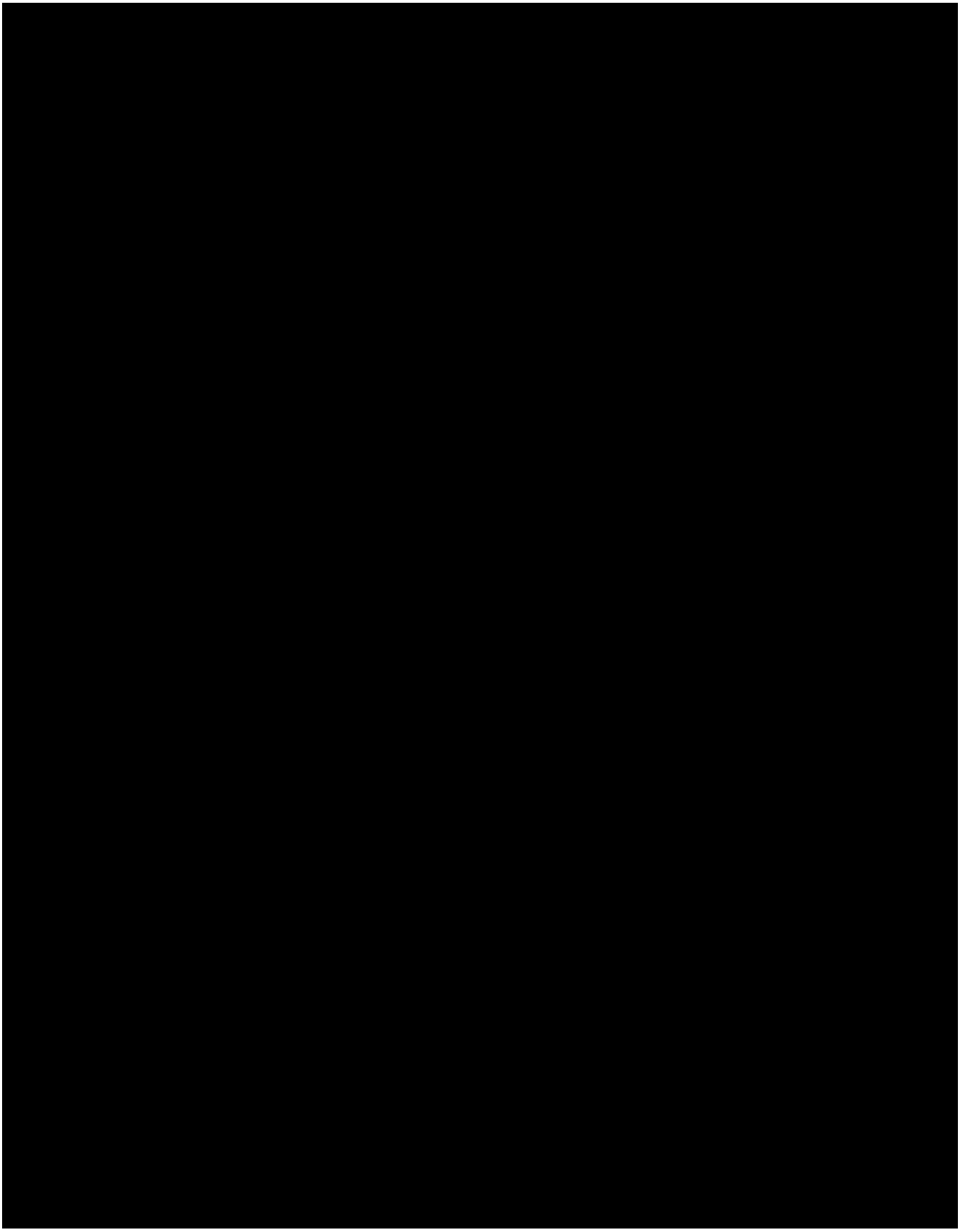


Figure 40: Subgroup analysis of OS in the PD-L1 ≥50% stage II–IIIA population

Clinical data cutoff: 21 January 2021. Abbreviations: BSC - best supportive care; CI - confidence interval; ECOG - Eastern Cooperative Oncology Group; eCRF - electronic case report form; IxRS -Interactive Voice/Web Response System; NE - not evaluable; NR - not reached. Figure available in EMA's assessment report [27].

Results per study

Table 72: Efficacy results of IMpower010 (NCT02486718) - PD-L1 TC ≥50%

				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 DFS	ATZ	115	NE (42.3-NE)	N/A	N/A	N/A	HR: 0.43	0.27-0.68	0.0012	HR was estimated by a Cox regression model, including two-sided 95% CIs. The stratified HR is presented here. Treatment comparisons were based on the stratified log-rank test. Median DFS was estimated by Kaplan-Meier methodology, and the Brookmeyer-Crowley method was used to establish the 95% CIs.	CCOD: Jan 21, 2021. Median follow-up: 34.2 mo. [19,27,32]
	BSC	114	35.7 mo. (29.7-NE)								
DFS rate at 3 years	ATZ	115	73.8% (64.4-83.2)	25.2%	11.0-39.4	0.0005	N/A	N/A	N/A	3-year landmark DFS rate was estimated by Kaplan-Meier methodology, and the Greenwood's formula were used to establish the 95% CIs.	CCOD: Jan 21, 2021. Median follow-up: 34.2 mo. [27]
	BSC	114	48.6% (38.0-59.2)								
DFS rate at 5 years	ATZ	115	NE	NE	NE	NE	N/A	N/A	N/A	5-year landmark DFS rate was estimated by Kaplan-Meier methodology, and the Greenwood's formula were used to establish the 95% CIs.	CCOD: Jan 21, 2021. Median follow-up: 34.2 mo. [27]
	BSC	114	NE								
Median OS	ATZ	115	NE (NE-NE)	NE	NE	NE	HR: 0.37	0.18-0.74	0.0089	Same methodology as applied for DFS. The unstratified HR is presented here.	CCOD: Jan 21, 2021. Median

	BSC	114	NE (NE-NE)								follow-up: 34.2 mo. [27]
OS rate at 3 years	ATZ	115	90.9% (85.2-96.7)	14.3%	4.2-24.4	0.0055	N/A	N/A	N/A	Same methodology as applied for DFS.	CCOD: Jan 21, 2021. Median follow-up: 34.2 mo. [27]
	BSC	114	76.7% (68.4-85.0)								
OS rate at 5 years	ATZ	115	NE	NE	NE	NE	N/A	N/A	N/A	Same methodology as applied for DFS.	CCOD: Jan 21, 2021. Median follow-up: 34.2 mo. [27]
	BSC	114	NE								