Medicinrådet

Bilag til Medicinrådets anbefaling vedr. atezolizumab til førstelinjebehandling af voksne patienter med uhelbredelig ikke-småcellet lungekræft, som ikke er egnede til behandling med platinbaseret kemoterapi

Vers. 1.0

Bilagsoversigt

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

Til Medicinrådet

Høringssvar fra Roche Pharmaceuticals vedrørende Medicinrådets udkast til vurdering af Tecentriq (atezolizumab) til behandling af førstelinje patienter med ikke-småcellet lungekræft som ikke tåler platinbaseret kemoterapi.

Roche Pharmaceuticals takker for det fremsendte udkast til vurderingsrapporten vedrørende Tecentriq (atezolizumab), som vi modtog d. 14. maj 2025. Vi har følgende kommentarer til vurderingsrapporten:

Overførbarhed af studiedata til dansk klinisk praksis

I udkastet til vurderingsrapporten fra Medicinrådet problematiseres overførbarheden af IPSOS-studiet til dansk klinisk praksis, og Medicinrådet ønsker at se en sammenligning af atezolizumab med platinbaseret kemoterapi. Selvom, at en sådan analyse kan være spændende, er den ikke relevant for den aktuelle vurdering.

IPSOS-studiet sammenligner effekten af atezolizumab med enkeltstof kemoterapi hos patienter, der ikke tåler platinbaseret kemoterapi. Det er derfor ikke hensigtsmæssigt at diskutere effekten hos patienter, som tåler platinbaseret kemoterapi, i denne vurdering, da det netop drejer sig om patienter der ikke tåler platinbaseret kemoterapi. Vi mener derfor, at Medicinrådets kritik vedrørende overførbarheden til dansk klinisk praksis er urimelig, og at den skyldes, at Medicinrådet ikke behandler ansøgningen i overensstemmelse med EMA's indikationsområde. Atezolizumabs indikation baseret på IPSOS studiet, er beskrevet nedenfor.

Generelt, udføres der meget begrænset randomiserede studier blandt skrøbelige patienter, og patienter med komorbiditeter, da dette er et heterogen gruppe. Derfor er immunterapi ligeledes, for nuværende, kun anbefalet blandt patienter med PS 0-1. Det efterlader en gruppe patienter, som IPSOS-studiet har vist også kan have fordel af immunterapi, da de ikke tåler platinbaseret kemoterapi. Som beskrevet i ansøgningen behandles en del af NSCLC patienter, som er uegnede til platinbaseret kemoterapi (med performance status 2 eller Charlson Comorbiditets Index 2 eller højere), allerede med immunterapi som monoterapi [1]. Dette indikerer, at sammenligningen i IPSOS-studiet faktisk kan være relevant i den danske kliniske praksis, i modsætning til hvad Medicinrådet beskriver. Dette bekræftes yderligere af danske læger som netop påpeger, at 4 serier vinorelbine anvendes til patienter der ikke tåler platinbaseret kemoterapi [2].
Atezolizumabs indikation baseret på IPSOS studiet [3].

Tecentriq er som enkeltstofbehandling indiceret til førstelinjebehandling af voksne patienter med fremskreden NSCLC, som ikke er egnede til platinbaseret behandling (se pkt. 5.1 for udvælgelseskriterier).

Følgende udvælgelseskriterier definerer patienter, der ikke er egnede til platinbaseret kemoterapi, og som er inkluderet i den terapeutiske indikation:

- *Patienter over 80 år, eller*
- *med en ECOG performance status (PS) på 3, eller*
- *patienter med en ECOG PS 2 i kombination med relevante komorbiditeter, eller*
- *ældre (≥ 70 år) i kombination med relevante komorbiditeter.*

Relevante komorbiditeter er relateret til hjertesygdomme, sygdomme i nervesystemet, psykiatriske sygdomme, vaskulære sygdomme, nyresygdomme, metaboliske og ernæringsmæssige sygdomme eller lungesygdomme, der er kontraindicerende for behandling med platinbaseret behandling, som vurderet af den behandlende læge.

Sikkerhed

Vi mener, at Medicinrådets præsentation af data vedr. sikkerhed i vurderingsrapporten er meget forsimplet. Vi har følgende kommentarer til afsnittet om bivirkninger:

- Det er rigtigt, som I skriver, at der er en numerisk højere værdi af patienter med alvorlige uønskede hændelser i atezolizumab armen. Ser man i IPSOS studiet, er der rapporteret en højere andel af relaterede alvorlige bivirkninger i kemoterapi armen, end i atezolizumab armen (16% vs. 12%) [4].
  Vi mener ikke, det er retvisende kun at præsentere alvorlige uønskede hændelser alene.
- Tilsvarende er der heller ikke præsenteret relaterede uønskede bivirkninger af grad 3 eller 4, hvor der også er en højere grad af relaterede bivirkninger ved kemoterapi end atezolizumab (33% vs. 16%). Vi mener ikke, at det er retvisende kun at præsentere patienter med uønskede hændelser af grad > 3 alene [4].
- Der er også langt flere patienter i kemoterapi armen, som oplever dosisreduktion eller pausering, sammenlignet med atezolizumab armen (48% vs. 32%) [4].
- Der er forskel i eksponeringen mellem atezolizumab armen og kemoterapi armen, hvilket også bør tages i betragtning i gennemgangen [4].
- I Bjørnhart et al. konkluderer de at IPSOS studiet viser, at atezolizumab har en favorabel bivirkningsprofil i forhold til kemoterapi [5]

Referencer

1. Mouritzen, et al. Nationwide survival benefit after implementation of first-line immunotherapy for patients with advanced NSCLC—real world efficacy. Cancers 13. 19, 2021.
2. Udsagn E fra ansøgningen.
3. EMA. “Tecentriq SmPC.” European Medicines Agency, https://www.ema.europa.eu/en/documents/product-information/tecentriq-epar-product-information_en.pdf. Accessed 21 May 2025.
4. Lee, et al. First-line atezolizumab monotherapy versus single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen (IPSOS): a phase 3, global, multicentre, open-label, randomised controlled study. vol. 402, The Lancet, 2023. 10400 vols.
5. Bjørnhart, et al. “5-Year survival in Danish patients with advanced non-small cell lung cancer treated with immune checkpoint inhibitor monotherapy.” Acta Oncologica, vol. 62, no. 8, 2023, pp. 861-870.

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20.05.2025

DBS/KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	Juni 2025 (skriftlig godkendelse)
Leverandør	Roche
Lægemiddel	Tecentriq (atezolizumab)
Ansøgt indikation	Tecentriq som monoterapi til førstelinjebehandling af voksne patienter med fremskreden ikke-småcellet lungekræft (NSCLC), som ikke er egnede til platinbaseret behandling
Nyt lægemiddel / indikationsudvidelse	indikationsudvidelse

Prisinformation

Amgros har følgende aftalepris på Tecentriq (atezolizumab):

Tabel 1: Aftalepris

Lægemiddel	Styrke	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Tecentriq	1.875 mg, 1 stk.	28.577,15	10.986,46	61,6%
Tecentriq	1.200 mg, 1 stk.	28.952,64	10.992,09	62,0%
Tecentriq	840 mg, 1 stk.	20.265,86	7.342,52	63,8 %

Aftaleforhold

[redacted]

[redacted]

[redacted]

Konkurrencesituationen

Patientpopulationen i ansøgningen har ikke tidligere været behandlet i Medicinrådet.

Tabel 1: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke og pakningsstr.	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Tecentriq	840 mg 1 stk. konc. t. infusion	1.680 mg i.v. hver 4. uge	[redacted]	[redacted]
Tecentriq	1.875 mg 1 stk. injektionsvæske, opløsning	1.875 mg s.c. hver 3. uge	[redacted]	[redacted]

Status fra andre lande

Tabel 2: Status fra andre lande

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

Opsummering:

[redacted]

Application for the assessment of Tecentriq (atezolizumab) for first-line treatment in patients with platinum-ineligible advanced Non-small cell lung cancer

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

Contact information

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Abbreviations

AESI	Adverse Event of Special Interest
AE	Adverse Event
ALK	Anaplastic lymphoma kinase
CCOD	Clinical Cut-Off Date
CCI	Charlson's Comorbidity Index
COPD	Chronic Obstructive Pulmonary Disease
DoR	Duration of Response
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5-dimension, 5-level questionnaire
ES-SCLC	Extensive-Stage Small Cell Lung Cancer
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
ICI	Immune checkpoint inhibitors
IPSOS	The phase III study of first-line atezolizumab monotherapy versus single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen

ITT	Intention to Treat
IV	Intravenous
KM	Kaplan-Meier
NSCLC	Non-small-cell lung cancer
ORR	Objective Response Rate
OS	Overall Survival
PD-L1	Programmed Cell Death Ligand 1
PFS	Progression-free Survival
PRO	Patient-reported Outcomes
QLQ-C30	Quality-of-life Questionnaire Core 30
QLQ-LC13	Quality-of-life Questionnaire Lung Cancer Module
RECIST	Response Evaluation Criteria in Solid Tumours
RWD	Real-world Data
SAE	Serious Adverse Event
SC	Subcutaneous
SmPC	Summary of product characteristics
TC	Tumour Cells
TNBC	Triple Negative Breast Cancer
TTD	Time-to detoriation
1L	First-line treatment
2L	Second-line treatment
95% CI	95% Confidence Interval

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Tecentriq
Generic name	Atezolizumab
Therapeutic indication as defined by EMA	Tecentriq as monotherapy is indicated for the first-line (1L) treatment of adult patients with advanced Non-small cell lung cancer (NSCLC) who are ineligible for platinum-based therapy (see section 5.1 for selection criteria in the Summary of product characteristics (SmPC)).
Marketing authorization holder in Denmark	Roche Pharmaceutical A/S
ATC code	L01FF05
Combination therapy and/or co-medication	Not applicable
(Expected) Date of EC approval	June 10th 2024
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	For the full description of each indication, please the the Tecentriq SmPC (1).All indications are provided in Appendix K. • **Early-stage non-small cell lung cancer** ○ Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have Programmed Cell Death Ligand 1 (PD-L1) expression on ≥ 50% of tumour cells (TC) and who do not have Epidermal Growth Factor Receptor (EGFR) mutant or Anaplastic lymphoma kinase(ALK)-positive NSCLC (see section 5.1 in SmPC for selection criteria). • **Metastatic NSCLC** ○ Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the 1L treatment of

	adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or 3 ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies (see section 5.1 in SmPC). ○ Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for the 1L treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1 in SmPC). ○ Tecentriq as monotherapy is indicated for the 1L treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1 in SmPC). ○ 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 (see section 5.1 in SmPC). • **Small cell lung cancer (SCLC**) ○ Tecentriq, in combination with carboplatin and etoposide, is indicated for the 1L treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) (see section 5.1 in SmPC).
Other indications that have been evaluated by the DMC (yes/no)	All indications are provided Appendix L. • **UC** ○ Tecentriq for use in patients with performance status 0-2 with PD-L1-expression >5% who are not eligible for cisplatin-based chemotherapy (recommended). Tecentriq for use in patients with performance status 0-1 with progression of disease after platinum-based therapy (recommended) (2). • **NSCLC** ○ Tecentriq as monotherapy after complete resection and platinum-based therapy in adult patients with a high risk of disease recurrence (PD-L1 ≥50%, no EGFR mutations, no ALK-positive NSCLC) (recommended) (3-5). • **SCLC** ○ Tecentriq in combination with carboplatine and etopside (ongoing) (6, 7). • **HCC** ○ Tecentriq in combination with Avastin as adjuvant treatment (ongoing). Tecentriq in combination with Avastin as 1L treatment (recommended) (8). • **TNBC**

	○ Tecentriq in combination with nab-paclitaxel for locally progressed or metastatic TNBC (PD-L1 IC ≥1) (recommended) (9).
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No Is the product suitable for a joint Nordic assessment? No If no, why not? Because it is already reimbursed and implemented in Sweden and the other Nordic countries do not need to apply for this indication
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	1 vial - 840 mg/14 mL for infusion 1 vial - 1200 mg/20 mL for infusion 1 vial - 1875 mg/15 mL for injection

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Tecentriq as monotherapy is indicated for the 1L treatment of adult patients with advanced NSCLC who are ineligible for platinum-based therapy (1). The selection criteria for "platinum-ineligibility" are: • Patients >80 years of age, or • Patients with an ECOG performance status of 3, or • Patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) 2 in combination with relevant comorbidities, or • Patients of older age (≥70 years) in combination with relevant comorbidities. Relevant comorbidities are related to renal, cardiac, vascular, nervous system, pulmonary, metabolism and nutrition, or psychiatric disorders contraindicating treatment with platinum-based therapy, as assessed by the treating physician.
Dosage regiment and administration	Intravenous: • 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks

	Until disease progression or unmanageable toxicity Subcutaneous: • 1 875 mg every 3 weeks Until disease progression or unmanageable toxicity
Choice of comparator	Single-agent chemotherapy (vinorelbine or gemcitabine) For squamous and non-squamous NSCLC patients the Danish lung cancer guidelines only describe platinum-based doublet chemotherapy (1). Clinical experts state that platinum-ineligible NSCLC patients in Denmark are treated with vinorelbine as monotherapy (10). The Danish lung cancer group states that NSCLC patients treated with platinum based doublet chemotherapy in 1L have a median overall survival (OS) of 10 months (1). It is expected that patients in 1L mono chemotherapy would have shorter median OS.
Prognosis with current treatment (comparator)	Platinum-ineligible NSCLC patients have limited treatment options due to performance status and comorbidities. Therefore these patients also have limited median OS
Type of evidence for the clinical evaluation	Head-to-head study
Most important efficacy endpoints (Difference/gain compared to comparator)	Median Overall Survival (OS) Atezolizumab: 10.3 months (95% CI: 9.4, 11.9) Chemotherapy: 9.2 months (95% CI: 5.9, 11.2) Hazard Ratio (HR): 0.78 (95% CI: 0.63, 0.97) 24-month rate Atezolizumab: 24% (95% CI: 19.3, 29.4) Chemotherapy: 12% (95% CI: 6.7, 18.0) Difference: 11.9% (95% CI: 4.4, 19.5) Investigator assessed median Progression-Free Survival (PFS) Atezolizumab: 4.2 months (95% CI: 3.7, 5.5) Chemotherapy: 4.0 months (95% CI: 2.9, 5.4) HR: 0.87 (95% CI: 0.70, 1.07) Objective Response Rate (ORR) Atezolizumab: 16.9% Chemotherapy: 7.9% HR: 8.9% (95% CI: 2.4, 15.5) Duration of Response (DoR) Atezolizumab: 14.0 months (95% CI: 8.1, 20.3) Chemotherapy: 7.8 months (95% CI: 4.8, 9.7)
Most important serious adverse events for the intervention and comparator	Pneumonia Atezolizumab: 11.0% Chemotherapy: 7.5%

Impact on health-related quality of life	No significant difference in QoL based on EORTC QLQ-C30 and EQ-5D-VAS.
Type of economic analysis that is submitted	N/A
Data sources used to model the clinical effects	N/A
Data sources used to model the health-related quality of life	N/A
Life years gained	N/A
QALYs gained	N/A
Incremental costs	N/A
ICER (DKK/QALY)	N/A
Uncertainty associated with the ICER estimate	N/A
Number of eligible patients in Denmark	Incidence: N/A Prevalence: N/A
Budget impact (in year 5)	N/A

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

3.1 The medical condition

Lung cancer is the most deadly cancer disease in Denmark. In 2022, 5043 Danish patients were diagnosed with lung cancer making the disease one of the most frequent cancer diseases (11, 12). More than 80% of the diagnosed patients have NSCLC and among these patients, approximately 50% locally advanced (stage III) or metastatic (stage IV) disease at the time of diagnosis.

Due to the fact that the primary reason for lung cancer is smoking, many lung cancer patients have a history of smoking or are still smoking. Given the age at the onset of the disease, and that lung cancer is not the only disease associated with smoking; patients with lung cancer often have other comorbidities e.g. Chronic Obstructive Pulmonary Disease (COPD), diabetes or kidney disease. This is also reflected in the high Charlson's Comorbidity Index (CCI) of around 40% in Danish Real-world data (RWD) studies in patients receiving monotherapy immune checkpoint inhibitors (ICI) (13, 14).

Current standard of care is either mono-immunotherapy or a combination of immunotherapy and chemotherapy depending on PD-L1 status (15). Immunotherapy are current only recommend for patients with ECOG PS 0-1 both as mono or combination therapy. If NSCLC patients are not candidates to immunotherapy due to comorbidities or ECOG PS 0-1 patients, they are offered platinum based chemotherapy combination with pemetrexed (15). If patients cannot get platinum-based chemotherapy, the Danish clinicians states that the remaining treatment options are monotherapy with vinorelbine or gemcitabine (10).

A large population of older patients cannot tolerate standard platinum-based chemotherapy due to their poorer performance status or substantial comorbidities (16). These patients are treated according to local guidelines, which includes less-effective single-agent chemotherapy or offered active supportive care, including palliative radiotherapy (17). Platinum-based chemotherapy doublets are recommended for older patients (≥70 years) with ECOG PS 0-1 (including some patients with a score of 2 who do not present with substantial comorbidities) (18, 19). Albeit, patients with a median age of 71 years and advanced NSCLC are excluded from the clinical trials due to poor performance status or have substantial comorbidities which are conferring ineligibility for standard platinum-based chemotherapy (20, 21).

However, single-agent chemotherapy is usually less efficacious prompting the investigation of new treatment options offering improved efficacy with an acceptable safety profile while maintaining quality of life in this underserved patient population (22-24).

In Bjørnhardt et al. they examined the use of ICI monotherapy in a Danish RWD setting, not only did they include ECOG PS 0-1, but also a subgroup of ECOG PS 2 patients (14). In this Danish RWD setting the study showed that in addition to PS 0-1 patients benefitting from ICI also ECOG PS 2 patients with high PD-L1 (≥50%) have long-term benefit of immunotherapy compared with palliative chemotherapy (14).

In another Danish nation-wide RWD for second-line (2L) or later ICIs in advanced NSCLC are descripted (13). The primary aim was to report OS in a Danish, comprehensive, consecutive population with advanced NSCLC, treated with ICIs in 2L or later line treatment. Underrepresented subgroups from randomized clinical trials was also included. 35% of the patients had a CCI score of mild or higher. The study showed that ICI should not be excluded based on chronological high age and that patients with ECOG PS ≥2 had limited effect in second or later lines (13). Thus underlining the benefit of treating "more frail" patients with the most efficient treatment early on.

3.2 Patient population

As mentioned above patients with metastatic NSCLC without driver mutations have the following standard of care options in Denmark, either monotherapy immunotherapy, or combination therapy with immunotherapy and chemotherapy, or platinum-based chemotherapy if the patients are not suitable for immunotherapy (15). As an estimate of the candidates, based on the indication and the yearly reports from 2019 and until the newest from 2022 from the Danish lung cancer group, the focus are ECOG PS 2 patients with NSCLC that would not be candidates for platinum-based chemotherapy (Table 1) (11, 25, 26). From 2019-2022 approximately 16% had ECOG PS 2 NSCLC (11, 25, 26). In addition around 73% of stage IV NSCLC patients from 2018-2022 received oncologic treatment within 365 days of their diagnosis date (11).

Table 1 Incidence and prevalence in the past 5 years (11, 25, 27).

Year	2019	2020	2021	2022	2023
Incidence in Denmark	N/A*	50	50	50	N/A**
Prevalence in Denmark	N/A*	30	30	30	N/A**
Global prevalence ***	N/A	N/A	N/A	N/A	N/A

* Yearly report from Danish lung cancer group covers both 2019 and 2020. ** Newest yearly report from Danish lung cancer group is from 2022. *** For small patient groups, also describe the worldwide prevalence. N/A – not applicable.

The patient population relevant for this application covers the Tecentriq indication on IP-SOS: Tecentriq as monotherapy is indicated for the 1L treatment of adult patients with advanced NSCLC who are ineligible for platinum-based therapy (1).

The selection criteria for "platinum-ineligibility" are the following:

- Patients >80 years of age, or
- Patients with an ECOG performance status of 3, or
- Patients with an ECOG PS 2 in combination with relevant comorbidities, or
- Patients of older age (≥70 years) in combination with relevant comorbidities.

Relevant comorbidities are related to renal, cardiac, vascular, nervous system, pulmonary, metabolism and nutrition, or psychiatric disorders contraindicating treatment with platinum-based therapy, as assessed by the treating physician.

The estimated number of patients eligible for treatment are listed in Table 2. These assumptions are based on the abovementioned estimates (11, 25, 27). It is also given that there at more elderly in the Danish population in general in the coming years, a small increase in the estimated number of patients eligible is expected.

Table 2 Estimated number of patients eligible for treatment.

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	50	50	55	55	60

3.3 Current treatment options

Current standard of care is either mono-immunotherapy or a combination of immunotherapy and chemotherapy depending on PD-L1 status (15). Immunotherapy are currently only recommended for patients with ECOG PS 0-1 both as mono- or combination therapy. If NSCLC patients are not candidates to immunotherapy due to comorbidities or ECOG PS 0-1 patients, the standard of care is platinum based chemotherapy combination (15). If patients cannot tolerate platinum-based chemotherapy either, the remaining treatment options are monotherapy with vinorelbine or gemcitabine (10).

3.4 The intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Tecentriq as monotherapy is indicated for the 1L treatment of adult patients with advanced NSCLC who are ineligible for platinum-based therapy (see section 5.1 for selection criteria) (1).

ATMP	No
Method of administration	Intravenous (IV) or subcutaneous (SC) (1)
Dosing	IV: 840 mg every 2 weeks or 1 200 mg every 3 weeks or 1 680 mg every 4 weeks SC: 1875 mg every 3 weeks
Dosing in the health economic model (including relative dose intensity)	N/A
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Until disease progression or unmanageable toxicity
Necessary monitoring, both during administration and during the treatment period	Standard of care
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	Tecentriq 840 mg concentrate for solution for infusion atezolizumab Tecentriq 1 200 mg concentrate for solution for infusion atezolizumab Tecentriq 1 875 mg solution for injection atezolizumab

3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

As mentioned above 1L patients with metastatic NSCLC without driver mutations have the following standard of care options in Denmark, either monotherapy immunotherapy or combination therapy with immunotherapy and chemotherapy based on PD-L1 expression, or platinum-based chemotherapy if the patients are not suitable for immunotherapy (15, 28). Danish clinicians state that monotherapy with vinorelbine would be a treatment options for NSCLC patient that cannot tolerate platinum-based chemotherapy (10). Depending on the 1L treatment, the patients have received, the following 2L treatments: Immunotherapy or chemotherapy (platin-based, pemetrexed or docetaxel) is recommend in Denmark.

As mention in section 3.1, two Danish studies have examined the real world use of immunotherapy in NSCLC patients in DK (13, 14).

3.5 Choice of comparator(s)

Based on inputs from the Danish clinical experts, the standard of care for platinum-ineligible 1L NSCLC patients in Denmark is 4 cycles of vinorelbine and therefore we only describe vinorelbine as the comparator and not gemcitabine which was also included in the IPSOS study (10).

Overview of comparator	
Generic name	Vinorelbine
ATC code	L01CA04
Mechanism of action	Antineoplastic cytostatic drug from the vinca alkaloid family. Vinorelbine functions by binding to the microtubules inside the cells and inhibiting mitosis at metaphase through the interaction with tubulin. Microtubule is a pivotal component in the separation of the cell's DNA during cell division
Method of administration	Oral or IV
Dosing	Oral (29): First three doses: 60 mg/m2 body surface area once a week Continued dosing: After the third dose, it is recommended to increase the dose of vinorelbine to 80 mg/m² once a week, except for patients whose neutrophil count has dropped to <500/mm³ once or has been in the range of 500-1000/mm³ multiple times during the first three doses at 60 mg/m² (29). IV (30): As monotherapy, the dose is usually 25-30 mg/m² once weekly.
Dosing in the health economic model (including relative dose intensity)	N/A
Should the medicine be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	4 cycles (10)

Overview of comparator	
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	Oral: 1 capsule 20 mg, 1 capsule 30 mg or 1 capsule 80 mg IV: 1 ml concentrate for solution for infusion, 10 mg/ml 5 ml concentrate for solution for infusion, 10 mg/ml 10 x 1 ml concentrate for solution for infusion, 10 mg/ml

3.6 Cost-effectiveness of the comparator(s)

Mono-chemotherapy in 1L NSCLC have not been assessed by the DMC, however vinorelbine and gemcitabine are considered standard of care and cost-efficient.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 3 Efficacy outcome measures relevant for the application (31).

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS) IPSOS (20)	41.0 months (IQR 36.7–47.8)	OS defined as the time from randomization to death from any cause	Kaplan-Meier (KM) methodology will be used to construct survival curves by treatments arms. The median OS and corresponding 95% CI will be provided for each treatment arm.
Overall survival rates (OS rate) IPSOS (20)	6, 12, 18 and 24 months	OS defined as the time from randomization to death from any cause OS rates at 6, 12, 18 and 24 months	The rates of OS at various timepoints (i.e., every 6 months after randomization until 24 months) will be estimated by the KM methodology for each arm and the 95% CI will be calculated using Greenwood's formula. The 95% CIs for the difference in OS rates between the two arms will be estimated using

			the normal approximation method
Investigator-assessed progression free survival (PFS) IPSOS (20)	41.0 months (IQR 36.7–47.8)	PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1, or death from any cause, whichever occurs first	PFS is defined as the time (in months) between the date of randomization and the date of first documented disease progression or death, whichever occurs first. Disease progression will be determined based on investigator assessment using RECIST v1.1. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the randomization date plus 1 day
Investigator-assessed objective response rate (ORR) IPSOS (20)	41.0 months (IQR 36.7–47.8)	ORR, defined as overall response (partial response plus complete response), as determined by the investigator using RECIST v1.1	ORR is defined as the proportion of patients who had an objective response. The analysis population for ORR will be all randomized patients with measurable disease at baseline. An estimate of ORR and its 95% CI will be calculated using the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs between the two arms will be determined using the normal approximation to the binomial distribution. The ORR will be compared between the two arms using z-statistics and the normal approximation.
Duration of response (DoR) IPSOS (20)	41.0 months (IQR 36.7–47.8)	DoR is defined as the time from initial response to disease progression or death among patients who have experienced a complete or partial response during the study.	DoR is defined as the time from initial response to disease progression or death among patients who have experienced a complete or partial response during the study. Patients who have not progressed at the time of analysis will be censored at the time of the last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of

	a complete or partial response, DoR will be censored at the date of the first occurrence of a complete or partial response plus 1 day. DoR is based on a nonrandomized subset of patients (specifically, patients who achieve an objective response); therefore, formal hypothesis testing will not be performed for this endpoint.

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

Validity of outcomes
The primary endpoint OS in IPSOS are well-defined and golden standard endpoint within oncologic research. The secondary endpoints in IPSOS: 6-month, 12-month, 18-month and 24-month Landmark OS; investigator-assessed PFS; investigator-assessed ORR per RECIST 1.1 are also well defined and golden standard endpoints within oncologic research (32).

4. Health economic analysis

N/A

4.1 Model structure

N/A

4.2 Model features

N/A

Table 4 Features of the economic model

Model features	Description	Justification
Patient population	N/A	[N/A
Perspective	N/A	N/A
Time horizon	N/A	N/A
Cycle length	N/A	N/A
Half-cycle correction	N/A	N/A
Discount rate	N/A	N/A

Intervention	N/A	N/A
Comparator(s)	XX	N/A
Outcomes	N/A	N/A

5. Overview of literature

5.1 Literature used for the clinical assessment

One study are relevant for this application namely: First-line atezolizumab monotherapy versus single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen (IPSOS). The study is a phase 3, global, multicentre, open-label, randomised controlled study that provides a comparison between 1L atezolizumab monotherapy versus single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen. Hence, a systematic literature review has not been performed.

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

Reference	Trial name	NCT identifier	Dates of study (33, 34)	Used in comparison of
Full paper: Lee, Siow Ming, et al. First-line atezolizumab monotherapy versus single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen (IPSOS): a phase 3, global, multicentre, open-label, randomised controlled study. The Lancet. 2023 Jul; 402(10400): 451-463. (20)	IPSOS	NCT03191786	Start: 11/09/17 Completion: 25/10/23 Data cut-off 30/04/22	Atezolizumab monotherapy vs. single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen
Conference abstract: Lee, Siow Ming, et al. IPSOS: Results from a Phase 3 study of first-line (1L) atezolizumab (atezo) vs single-agent chemotherapy (chemo) in patients (pts) with NSCLC not eligible for a platinum-containing regimen. Presented at ESMO Congress in Paris 2022. (33)	IPSOS	NCT03191786	Start: 11/09/17 Completion: 25/10/23 Data cut-off 30/04/22	Atezolizumab monotherapy vs. single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen
Data on file Unpublished data 2023. Atezolizumab Clinical Study Report. (23)	IPSOS	NCT03191786	Start: 11/09/17 Completion: 25/10/23 Data cut-off 30/04/22	Atezolizumab monotherapy vs. single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen

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

Table 6 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference	Health state/Disutility	Reference to where in the application the data is described/applied
Full paper: Lee, Siow Ming, et al. First-line atezolizumab monotherapy versus single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen (IPSOS): a phase 3, global, multicentre, open-label, random-ised controlled study. The Lancet. 2023 Jul; 402(10400): 451-463. (20)	Platinum ineligible 1L metastatic NSCLC	In section 10
Data on file Unpublished data 2023. Atezolizumab Clinical Study Report. (23)	Platinum ineligible 1L metastatic NSCLC	In section 10

5.3 Literature used for inputs for the health economic model

N/A

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

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

6. Efficacy

6.1 Efficacy of first-line atezolizumab monotherapy compared to single-agent chemotherapy for patients with NSCLC ineligible for a platinum-containing regimen

6.1.1 Relevant studies

IPSOS is a phase III, open-label, randomised controlled study done at 91 sites in 23 countries across Asia, Europe, North America, and South America designed to evaluate the efficacy and safety of 1L atezolizumab monotherapy compared with a standard single-agent chemotherapy (gemcitabine or vinorelbine) in patients with locally advanced or metastatic NSCLC, for whom platinum-doublet chemotherapy was deemed unsuitable by the investigator (20).

Eligible patients had stage IIIB NSCLC that was not amenable to multimodality radical treatment or stage IV NSCLC, per the American Joint Committee on Cancer staging system 7th edition. Patients were deemed platinum-ineligible by the investigator if they had an ECOG PS 2-3 or were aged ≥70 years with substantial comorbidities or other contraindications for any platinum-doublet chemotherapy. Patients whose tumors were positive for EGFR (Leu858Arg or exon 19 deletion) or ALK alterations were excluded. Patients with treated, asymptomatic brain metastases were permitted.

Patients were randomized in the ratio 2:1 by permuted-block randomization (block size of six) to receive 1200 mg of atezolizumab IV Q3W on day 1 of each cycle or single-agent chemotherapy (vinorelbine [oral or IV] or gemcitabine [IV]; dosing per local label) at Q3W or Q4W cycles. The 2:1 randomization enabled more safety data to be gathered in a poor prognosis (i.e., ECOG PS 2–3), older group with comorbidities. Randomization was stratified by histological subtype, brain metastases and PD-L1 expression level according to the SP142 immunohistochemistry assay (Figure 1). Amount of patients who continued atezolizumab treatment after disease progression (RECIST v 1.1) and subsequent treatments according to Figure 1 can be found in Table 59 (Appendix M).

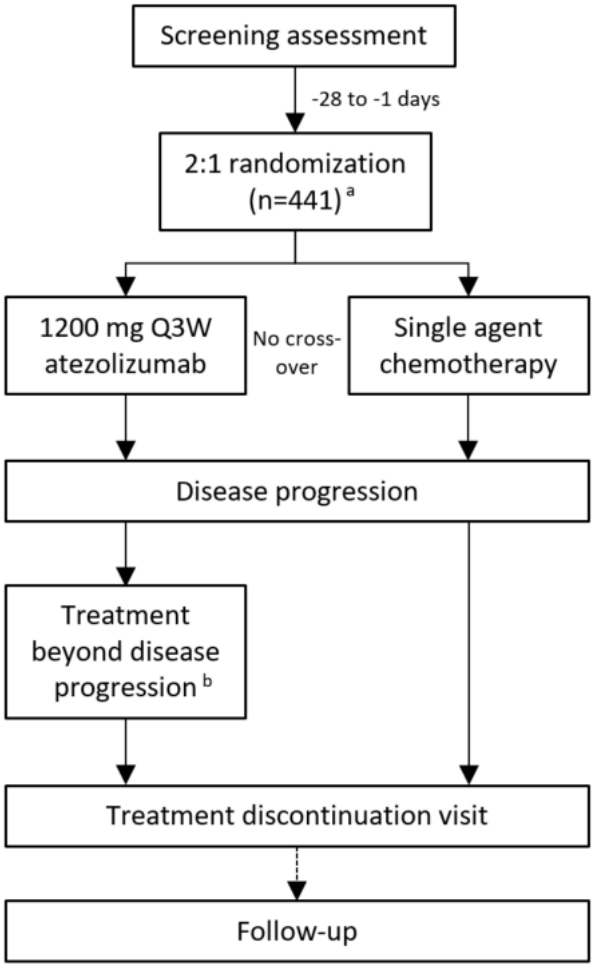

Figure 1 IPSOS Study Schema. [a] 2:1 Randomization was stratified by histology (non-squamous vs. squamous), PD-L1 status by immunohistochemistry and Brain metastases (yes/no). [b] Patients in the experimental arm with atezolizumab who show evidence of clinical benefit, may continue atezolizumab treatment after disease progression (RECIST v 1.1) if they meet criteria specified in the protocol per investigator's discretion (31).

Atezolizumab treatment was permitted to be continued beyond disease progression according to RECIST 1.1 until loss of clinical benefit, unacceptable toxicity, patient or physician decision to discontinue, or death. Unacceptable toxicity was defined as any intolerable toxicity related to atezolizumab treatment (including development of an immune-mediated adverse event (AE) determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event), intolerable toxicity related to chemotherapy treatment, or any medical condition that could jeopardize the patient's safety if they continued study treatment.

Patients in the chemotherapy arm received treatment with single-agent chemotherapy (i.e., vinorelbine [orally or IV] or gemcitabine [IV]; dosing per local label) based on approval in their country and investigator's choice. Chemotherapy was administered at Q3W or Q4W cycles per relevant local PI or SmPC until disease progression per RECIST 1.1. No cross-over was allowed between treatment arms.

All patients were followed up until the clinical cut-off date (CCOD). The duration of follow-up is calculated using the elapsed time between the randomization and the last date a patient is known to have been alive or to have died.

The primary efficacy endpoint was the comparison of OS between the two groups in the intention-to-treat (ITT) population. Secondary efficacy endpoints included OS rates at 6, 12, 18, and 24 months; investigator-assessed progression-free survival (PFS); OS and investigator-assessed PFS in patients with PD-L1 expressing tumors as identified by the SP263 immunohistochemistry assay; and ORR and DoR using RECIST 1.1. Other endpoints included patient-reported HRQoL outcomes. Safety analyses were conducted in the safety-evaluable population, which included all randomized patients who received any amount of atezolizumab or chemotherapy.

More information on the study used can be found in Table 8.

Table 8 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
IPSOS, NCT03191786 (20)	Phase III, open-label, randomised controlled study designed to evaluate the efficacy and safety of first-line atezolizumab monotherapy compared with a standard single-agent chemotherapy (gemcitabine or vinorelbine).	Patients were randomised 2:1 by permuted-block randomisation (block size of six) to receive 1200 mg of atezolizumab given intravenously every 3 weeks or single-agent chemotherapy (vinorelbine [oral or IV] or gemcitabine [IV]; dosing per local label) at 3-weekly or 4-weekly cycles. **Atezolizumab duration**: until loss of clinical benefit, unacceptable toxicity, participant or physician decision to discontinue, or death. **Chemotherapy duration**: until disease progression per RECIST 1.1. No crossover was allowed between treatment groups.	Patients with locally advanced or metastatic NSCLC, for whom platinum-doublet chemotherapy was deemed unsuitable by the investigator.	Atezolizumab (IV administration), 1200 mg on Day 1 of each 21-day cycle until loss of clinical benefit, unacceptable toxicity, participant or physician decision to discontinue, or death.	Single-agent chemotherapy (vinorelbine [oral or IV] or gemcitabine [IV], dosing per local label) at 3-weekly or 4-weekly cycles.	Outcomes: The primary efficacy endpoint was the comparison of overall survival between the two arms in the ITT population. Secondary efficacy endpoints included OS rates at 6, 12, 18, and 24 months; investigator-assessed PFS; OS and investigator-assessed PFS in patients with PD-L1 expressing tumours as identified by the SP263 immunohistochemistry assay; and ORR and DoR using RECIST 1.1. Other endpoints included patient-reported HRQoL outcomes and safety. Follow-up period: Follow-up data, including subsequent non-protocol anticancer therapies, continued to be collected for each patient until death, withdrawal of consent, loss to follow-up, or study termination by the sponsor, whichever occurred first.

6.1.2 Comparability of studies

N/A.

This section is not relevant as efficacy and safety are compared directly in the IPSOS study.

6.1.2.1 Comparability of patients across studies

Baseline characteristics of patients in the IPSOS study are listed in Table 9. Generally, patient characteristics were well balanced between the atezolizumab and chemotherapy arms, respectively. Median patient age was 75 years in both arms. A total of 140 (31%) patients were age 80 years or older. The proportion of males was 73% and 72% in the atezolizumab arm and chemotherapy arm, respectively. Most patients were white in both arms namely 67% in the atezolizumab arm and 63% in the chemotherapy arm. In the atezolizumab arm, 75% of the patients had an ECOG PS of 2, 19% had a score of 0 or 1 and 6% had a score of 3. In the chemotherapy arm, 77% of the patients had an ECOG PS of 2, 13% had a score of 0 or 1 and 11% had a score of 3. A total of 69% (312 patients) had a history of previous tobacco use and 19% (86 patients in total) were currently using tobacco. 57% (173 patients) in the atezolizumab arm and 58% (87 patients) in the chemotherapy arm had a non-squamous histology. 43% (129 patients) in the atezolizumab arm and 42% (64 patients) in the chemotherapy arm had a squamous histology. Amount of patients with brain metastases were 9% (27 patients) in the atezolizumab arm and 9% (13 patients) in the chemotherapy arm. Patients without brain metastases were 90% (273 patients) in the atezolizumb arm and 91% (137 patients) in the chemotherapy arm. Median number of ongoing medical conditions per patient was 6 in the atezolizumab arm and 5 in the chemotherapy arm. 97% (293 patients) in the atezolizumab arm and 97% (146 patients) in the chemotherapy arm had one or more ongoing medical conditions. A higher proportion of patients (32%) in the atezolizumab arm had gastrointestinal disorders as ongoing medical condition compared to the chemotherapy arm (20%). Furthermore, in both treatment groups, 17% of patients had PD-L1–high tumours (ie, tumour cell ≥50%; SP263 assay). Compared with the chemotherapy group, the atezolizumab group had a higher prevalence of patients with PD-L1–negative tumours (ie, tumour cell <1%; 50% vs 40%; SP263 assay) and a lower prevalence of patients with PD-L1–low tumours (ie, tumour cell 1–49%; 25% vs 35%; SP263 assay).

Table 9 Baseline characteristics of patients in the IPSOS study (20).

	IPSOS	
	Atezolizumab N=302	**Chemotherapy N=151**
Age - Median (min-max)	75.0 (69.0-81.0)	75.0 (68.0-80.0)
Age group - n (%)		
≥80 years	97 (32%)	43 (28%)

IPSOS		
	Atezolizumab N=302	**Chemotherapy N=151**
70-79 years	125 (41%)	65 (43%)
<70 years	80 (26%)	43 (28%)
Gender - n (%)		
Male	220 (73%)	108 (72%)
Female	82 (27%)	43 (28%)
Race - n (%)		
White	203 (67%)	95 (63%)
Asian	75 (25%)	38 (25%)
Other	24 (8%)	18 (12 %)
ECOG PS - n (%)		
0 or 1	56 (19%)	19 (13%)
2	228 (75%)	116 (77%)
3	18 (6%)	16 (11%)
Tobacco use history - n (%)		
Previous	209 (69%)	103 (68%)
Current	58 (19%)	28 (19%)
Never	35 (12%)	20 (13%)
Histology - n (%)		
Non-squamous	173 (57%)	87 (58%)
Squamous	129 (43%)	64 (42%)
Stage - n (%)		
IIIB	41 (14%)	21 (14%)
IV	261 (86%)	130 (86%)

IPSOS		
	Atezolizumab N=302	**Chemotherapy N=151**
Brain metastases - n (%)		
Yes	27 (9%)	13 (9%)
No	273 (90%)	137 (91%)
Liver metastases - n (%)		
Yes	44 (15%)	26 (17%)
No	258 (85%)	125 (83%)
Number of metastatic sites - n (%)		
<3	124 (41%)	73 (48%)
≥3	141 (47%)	59 (39%)
Missing	37 (12%)	19 (13%)
***EGFR* mutation status - n (%)**		
Mutations other than Leu858Arg or exon 19 deletions	1 (<1%)	1 (1%)
No mutation	269 (89%)	131 (87%)
Not done	32 (11%)	19 (13%)
***ALK* rearrangement status - n (%)**		
No	266 (88%)	130 (86%)
Not evaluable	3 (1%)	1 (1%)
Not done	33 (11%)	20 (13%)
PD-L1 expression level by SP142 immunohistochemistry assay - n (%)		
TC0 and IC0	157 (52%)	79 (52%)
TC1/2/3 or IC1/2/3	130 (43%)	66 (44%)

IPSOS		
	Atezolizumab N=302	**Chemotherapy N=151**
TC2/3 or IC2/3	54 (18%)	40 (26%)
TC3 or IC3	18 (6%)	10 (7%)
Unknown*	15 (5%)	6 (4%)
PD-L1 expression level by SP263 immunohistochemistry assay - n (%)		
TC <1%	151 (50%)	61 (40%)
TC ≥1%	127 (42%)	78 (52%)
TC 1-49%	77 (25%)	53 (35%)
TC ≥50%	50 (17%)	25 (17%)
Unknown*	24 (8%)	12 (8%)
Ongoing medical conditions per patient - median (min-max)	6.0 (3.0-9.0)	5.0 (3.0-8.0)
Patients with ≥1 ongoing medical condition - n (%)	293 (97%)	146 (97%)
Respiratory, thoracic, and mediastinal disorders	198 (66%)	96 (64%)
Vascular disorders	179 (59%)	84 (56%)
Metabolism and nutrition disorders	155 (51%)	86 (57%)
Cardiac disorders	106 (35%)	51 (34%)
Musculoskeletal and connective tissue disorders	100 (33%)	54 (36%)
General disorders and administration site conditions	96 (32%)	54 (36%)
Gastrointestinal disorders	97 (32%)	30 (20%)
Nervous system disorders	60 (20%)	25 (17%)
Renal and urinary disorders	49 (16%)	20 (13%)

IPSOS		
	Atezolizumab N=302	**Chemotherapy N=151**
Psychiatric disorders	47 (16%)	21 (14%)
Blood and lymphatic system disorders	38 (13%)	29 (19%)
Reproductive system and breast disorders	47 (16%)	17 (11%)
Investigations	35 (12%)	22 (15%)
Endocrine disorders	32 (11%)	13 (9%)
Hepatobiliary disorders	27 (9%)	9 (6%)
Neoplasms benign, malignant, and unspecified**	25 (8%)	11 (7%)
Infections and infestations	23 (8%)	8 (5%)
Skin and subcutaneous tissue disorders	24 (8%)	6 (4%)
Eye disorders	20 (7%)	8 (5%)
Ear and labyrinth disorders	20 (7%)	7 (5%)
Immune system disorders	11 (4%)	5 (3%)
Social circumstances	11 (4%)	3 (2%)
Injury, poisoning, and procedural complications	10 (3%)	3 (2%)
Congenital, familial, and genetic disorders	4 (1%)	4 (3%)
Surgical and medical procedures	2 (1%)	0

Abbreviations: ECOG PS - Eastern Cooperative Oncology Group performance status score; PD-L1 - Programmed death-ligand 1;

*PD-L1 immunohistochemistry status could not be assessed.

**Including cysts and polyps.

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

Data for NSCLC patients in Denmark receiving 1L ICI are presented in Table 10. There are no general description of platinum-ineligible 1L NSCLC patients in Denmark. Data from Bjørnhardt et al. show that, of the 1L NSCLC patients 18% have PS2, 39% have a Charlson's index of 2 or above and that 29% was 75 years or above. This shows that some 1L platinum-ineligible NSCLC patients already receive monotherapy in accordance with the IPSOS indication (14).

Table 10 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (14)	Value used in health economic model (reference if relevant)
Median age (years), range	69 (39-92)	N/A
Age ≥75, n (%)	83 (29)	N/A
Gender Female, n (%)	177 (55)	N/A
PD-L1 TPS, n (%)		N/A
<0%	1 (0)	
<50%	11 (3)	
≥50%	309 (96)	
Missing	0	
Performance status (PS), n (%)		N/A
0	82 (26)	
1	180 (56)	
≥2	59 (18)	
Missing	0	
Charlson's Comorbidity Index (CCI), n (%)		N/A
0	100 (31)	
1	95 (30)	
≥2	126 (39)	
Distant metastatic site, n (%)	N=256	N/A
Brain	28 (9)	
Liver	30 (9)	
Adrenal gland	56 (17)	

Bone	94 (29)
Other	48 (15)

6.1.4 Efficacy – results per IPSOS

In this section, results on the following outcomes are presented from the IPSOS (MO29872) study (20):

- Primary endpoint
  - Overall survival in the ITT population
- Secondary endpoints
  - Overall survival rates at 6, 12, 18 and 24 months
  - Investigator-assessed progression-free survival
  - Overall survival and investigator-assessed progression-free survival in patients with PD-L1 expressing tumors as identified by the SP263 immunohistochemistry assay
  - ORR and DoR using RECIST 1.1.

Overall survival in the ITT population

OS was the primary efficacy outcome in IPSOS and defined as the time from randomization to death from any cause. Patients without a date of death was censored on the date a patient was last known to be alive. OS was censored at the date of randomization plus 1 day if there were no post-baseline data available. The primary efficacy analysis is the comparison of OS between the two treatment arms (atezolizumab arm and single agent chemotherapy arm). The OS was assessed using the Kaplan-Meier (KM) method to estimate survival curves for both treatment arms. The log-rank test was employed to compare OS between the groups, and a Cox proportional hazards model was used to calculate the HR and 95% confidence intervals (CIs), stratified by factors such as histology, brain metastasis status, and PD-L1 expression level (31). An interpretation of the Schoenfeld residual plot used to assess the plausibility of the proportional hazards assumption and Log of Negative Log of Estimated Survivor Function for OS and PFS can be found in Appendix B.

At the final analysis, an OS improvement with a median of 10.3 months (95% CI: 9.4, 11.0) was observed in the atezolizumab arm compared to the chemotherapy arm with a median of 9.2 months (95% CI: 5.9–11.2) in the ITT population. OS events occurred in 249 (82%) of 302 patients assigned to atezolizumab and 130 (86%) of 151 patients assigned to chemotherapy. The stratified HR was 0.78 (95% CI: 0.63, 0.97) with a p value of 0.028 showing an improvement in OS with atezolizumab. 2-year survival rates were 24.3% in the atezolizumab arm, compared to 12.4% in the chemotherapy arm (Figure 2)(20).

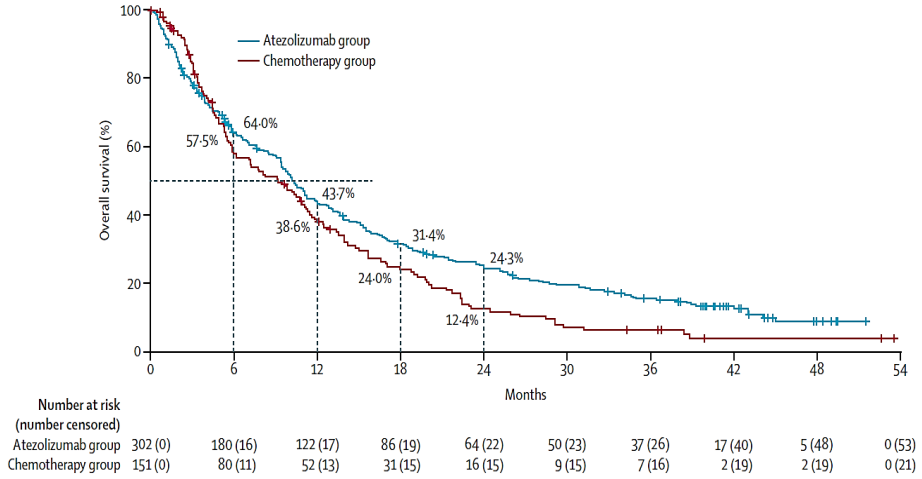

Figure 2 KM overall survival estimates in the intention-to-treat population. Dashed horizontal line shows 50% overall survival.

OS rates at 6, 12, 18 and 24 months

The OS rate at specific time points (6, 12, 18, and 24 months) was included to provide a detailed view of survival dynamics over time. OS rates at specific time points provided a clearer understanding of how survival benefits may evolve over time. The OS rates was assessed using the same method as for the primary efficacy outcome (31).

The OS rate in the ITT population at 6 months was 64% (95% CI: 58.6, 69.5) in the atezolizumab arm and 58% (95% CI: 49.4, 65.7) in the chemotherapy arm. At 12 months the OS rate was 44% (95% CI 37.9, 49.4) in the atezolizumab arm and 39% (95% CI: 30.5, 46.7) in the chemotherapy arm. At 18 months it was 31% (95% CI: 26.0, 36.8) in the atezolizumab arm and 24% (95% CI: 16.8, 31.2) in the chemotherapy arm. At 24 months the rates were 24% (95% CI: 19.3, 29.4) in the atezolizumab arm and 12% (95% CI: 6.7–18.0) in the chemotherapy arm (Table 11) (20).

Table 11 OS rates at 6, 12, 18 and 24 months (20).

Time point	Atezolizumab (n=302)	Chemotherapy (n=151)	Difference in OS rates
6-month rate	64% (95% CI: 58.6, 69.5)	58% (95% CI: 49.4, 65.7)	6.5% (95% CI: -3.3, 16.3)
12-month rate	44% (95% CI: 37.9, 49.4)	39% (95% CI: 30.5, 46.7)	5.1% (95% CI: -4.9, 15.0)
18-month rate	31% (95% CI: 26.0, 36.8)	24% (95% CI: 16.8, 31.2)	7.4% (95% CI: -1.6, 16.5)
24-month rate	24% (95% CI: 19.3, 29.4)	12% (95% CI: 6.7, 18.0)	11.9% (95% CI: 4.4, 19.5)

Investigator-assessed progression-free survival (PFS)

PFS was defined as time between date of randomization and date of first disease progression or death, whichever occurred first. Disease progression was based on investigator's assessment using RECIST v1.1. Patients who did not experienced disease progression or death at the time of analysis was censored at the time of last tumor assessment. Patients with no post baseline tumor assessment was censored at the randomization date plus 1 day (31).

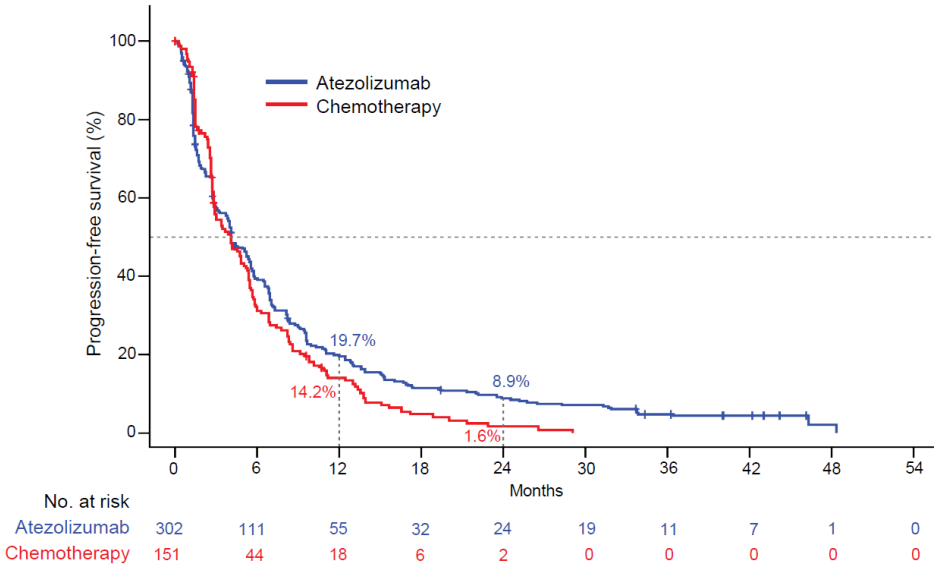

Figure 3 KM PFS estimates in the intention-to-treat population. Dashed horizontal line shows 50% PFS (33).

Median PFS was 4.2 months (95% CI: 3.7, 5.5) in the atezolizumab arm and 4.0 months (95% CI: 2.9, 5.4) in the chemotherapy arm with a stratified HR of 0.87 (95% CI: 0.70, 1.07). PFS rates at 12 months were 20% (95% CI: 15.0, 24.3) in the atezolizumab arm and 14% (95% CI: 8.3, 20.0) in the chemotherapy arm. 24 months PFS rates were 9% (95% CI: 5.5, 12.2) in the atezolizumab arm and 2% (95% CI: 0.0, 3.7) in the chemotherapy arm (20).

OS and investigator-assessed PFS in patients with PD-L1 expressing tumors as identified by the SP263 immunohistochemistry assay

OS events in the PD-L1-negative subgroup occurred in 129 (85.4%) of 151 patients assigned to atezolizumab and 52 (85.2%) of 61 patients assigned to chemotherapy. The median OS estimate for the PD-L1-negative subgroup was 10.3 months (95% CI: 9.3, 13.0) in the atezolizumab arm and 7.1 months (95% CI: 4.8, 11.9) in the chemotherapy arm with an unstratified HR of 0.81 (95% CI: 0.58, 1.11) (Figure 4). OS events in the PD-L1-positive subgroup occurred in 102 (80.3%) of 127 patients assigned to atezolizumab and 69 (88.5%) of 78 patients assigned to chemotherapy. The median OS estimate for the PD-L1-positive subgroup was 9.4 months (95% CI: 7.0, 11.3) in the atezolizumab arm and 10.3 months (95% CI: 7.1, 12.3) in the chemotherapy arm with an unstratified HR of 0.84 (95% CI: 0.62, 1.15) (Figure 5). In the PD-L1-low subgroup the unstratified HR was

0.84 (95% CI: 0.57, 1.22), 0.87 (95% CI: 0.50, 1.52) in the PD-L1-high subgroup and 0.49 (95% CI: 0.21, 1.14) in the PD-L1-unknown group (20).

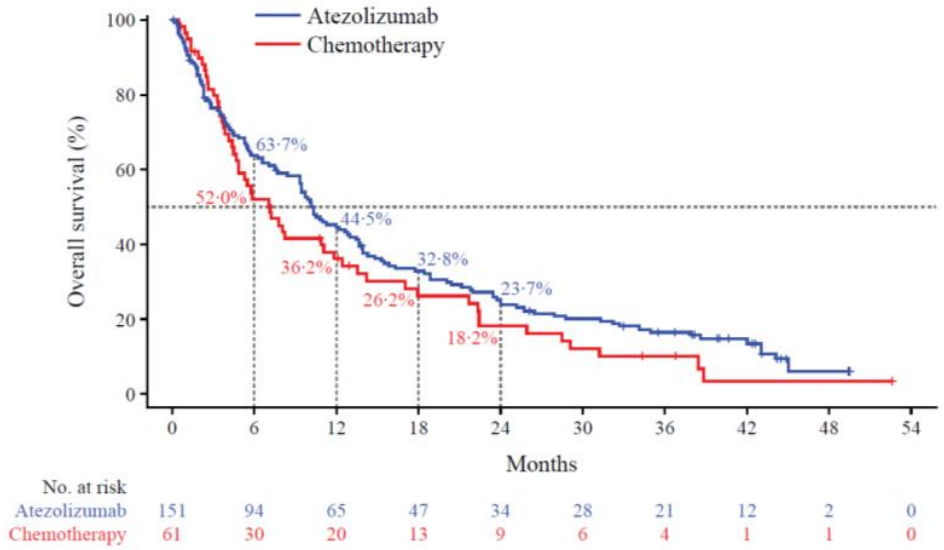

Figure 4 KM OS estimates in the intention-to-treat population for the PD-L1–negative subgroup (TC <1%), as assessed by the SP263 immunohistochemistry assay. OS=overall survival; TC=tumour cell.

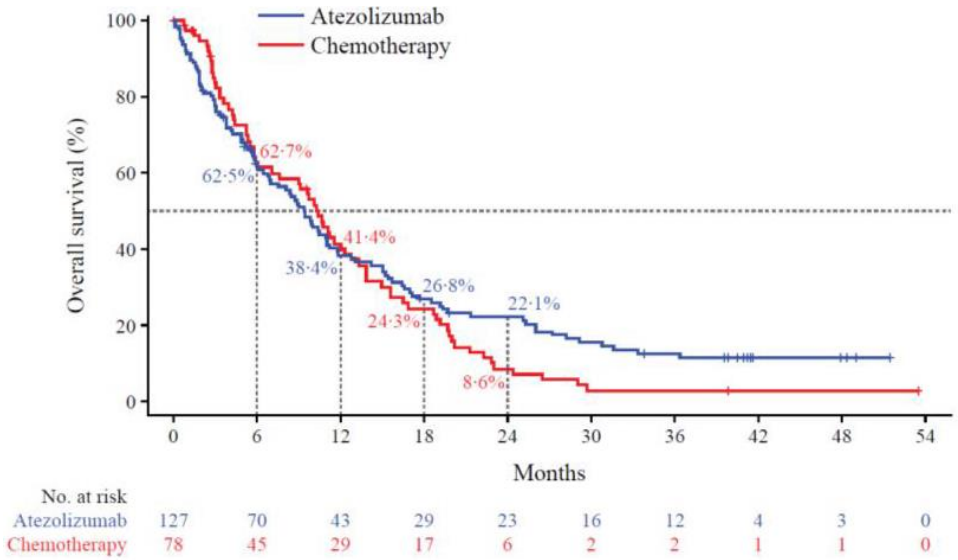

Figure 5 KM OS estimates in the intention-to-treat population for the PD-L1–positive subgroup (TC≥1%), as assessed by the SP263 immunohistochemistry assay. OS=overall survival; TC=tumour cell.

The unstratified OS HR for the ECOG PS subgroups was 0.64 (95% CI: 0.36, 1.13) for ECOG PS 0–1, 0.86 (95% CI: 0.67, 1.10) for ECOG PS 2, and 0.74 (95% CI: 0.35, 1.57) for ECOG PS 3. Across histology types, the unstratified OS HR was 0.77 (95% CI: 0.58, 1.03) for non-squamous and 0.80 (95% CI: 0.58, 1.12) for squamous histology (20).

The median PFS unstratified HRs across PD-L1 expression subgroups were 0.90 (95% CI: 0.66, 1.24) in the PD-L1–negative group, 0.83 (95% CI: 0.62, 1.12) in the PD-L1–positive group, 1.01 (95% CI: 0.69, 1.45) in the PD-L1–low group, and 0.64 (95% CI: 0.38, 1.08) in the PD-L1–high group (20).

Objective response rate (ORR) and Duration of response (DoR)

ORR was defined as the proportion of patients who had an objective response. The analysis population for ORR was all randomized patients that had a measurable disease at baseline. An estimate of ORR and its 95% CI was calculated using the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs between the two arms was determined using the normal approximation to the binomial distribution (31).

DoR was defined as the time from initial response to disease progression or death among patients who have experienced a complete or partial response during the study. Patients who did not progress at the time of analysis was censored at the time of the last tumor assessment date. If no tumor assessments was performed after the date of the first occurrence of a complete or partial response, DoR was censored at the date of the first occurrence of a complete or partial response plus 1 day. DoR is based on a non-randomized subset of patients (specifically, patients who achieve an objective response); therefore, formal hypothesis testing will not be performed for this endpoint (20).

Of patients who had an objective response, there were 51 (17%) of 302 patients (95% CI: 12.8, 21.6) in the atezolizumab arm and 12 (8%) of 151 patients (95% CI: 4.2, 13.5) in the chemotherapy arm. The median duration of response was 14.0 months (95% CI: 8.1, 20.3) in the atezolizumab arm and 7.8 months (95% CI: 4.8, 9.7) in the chemotherapy group (Table 12) (20).

Table 12 ORR and DoR in the ITT population (20).

	Atezolizumab (n=302)	Chemotherapy (n=151)
Objective Response	51 (17%) (95% CI: 12.8, 21.6)	12 (8%) (95% CI: 4.2, 13.5)
Complete response	4 (1%)	0
Partial response	47 (16%)	12 (8%)
Stable disease	122 (40%)	73 (48%)
Progressive disease	67 (22%)	36 (24%)
Non-evaluable	14 (5%)	12 (8%)
Missing	48 (16%)	18 (12%)
DoR		

	Atezolizumab (n=302)	Chemotherapy (n=151)
Number of responders	51	12
Median (95% CI), months	14.0 (95% CI: 8.1, 20.3)	7.8 (95% CI: 4.8, 9.7)

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

N/A.

7.1.2 Method of synthesis

N/A.

7.1.3 Results from the comparative analysis

Table 13 Results from the comparative analysis of atezolizumab vs. chemotherapy for patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen (20, 23).

Outcome measure	Atezolizumab (N=302)	Chemotherapy (N=151)	Result
Median Overall Survival (OS)	10.3 months (95% CI: 9.4, 11.9)	9.2 months (95% CI: 5.9, 11.2)	Difference: 1.1 HR: 0.78 (95% CI: 0.63, 0.97)
OS rate, 6-months	64% (95% CI: 58.6, 69.5)	58% (95% CI: 49.4, 65.7)	Difference: 6.5% (95% CI: -3.3, 16.3)
OS rate, 12-months	44% (95% CI: 37.9, 49.4)	39% (95% CI: 30.5, 46.7)	Difference: 5.1% (95% CI: -4.9, 15.0)
OS rates, 18-months	31% (95% CI: 26.0, 36.8)	24% (95% CI: 16.8, 31.2)	Difference: 7.4% (95% CI: -1.6, 16.5)
OS rates, 24-months	24% (95% CI: 19.3, 29.4)	12% (95% CI: 6.7, 18.0)	Difference: 11.9% (95% CI: 4.4, 19.5)
Median Progression-Free Survival (PFS), months	4.2 (95% CI: 3.7, 5.5)	4.0 (95% CI: 2.9, 5.4)	Difference: 0.2 HR: 0.87 (95% CI: 0.70, 1.07)

Outcome measure	Atezolizumab (N=302)	Chemotherapy (N=151)	Result
PFS, 12-months	20% (95% CI: 15.0, 24.3)	14% (95% CI: 8.3, 20.0)	[redacted]
PFS, 24-months	9% (95% CI: 5.5, 12.2)	2% (95% CI: 0.0, 3.7)	
Objective Response Rate (ORR)	17% (95% CI: 12.8, 21.6)	8% (95% CI: 4.2, 13.5)	
Complete response	4 (1%)	0	Difference: 1% NR
Partial response	47 (16%)	12 (8%)	Difference: 8% NR
Stable disease	122 (40%)	73 (48%)	Difference: -8% NR
Progressive disease	67 (22%)	36 (24%)	Difference: -2% NR
Non-evaluable	14 (5%)	12 (8%)	Difference: -3% NR
Missing	48 (16%)	18 (12%)	Difference: 4 % NR
Median Duration of Response (DoR)	14.0 months (95% CI: 8.1, 20.3)	7.8 months (95% CI: 4.8, 9.7)	Difference: 6.2 months NR

7.1.4 Efficacy – results per OS between the two arms in the ITT population

At the final analysis, OS events occurred in 249 (82%) of 302 patients assigned to atezolizumab and 130 (86%) of 151 patients assigned to chemotherapy. In the ITT population, an OS improvement was observed in the atezolizumab group (median OS 10.3 months [95% CI: 9.4, 11.9]) compared with the chemotherapy group (median OS 9.2 months [95% CI: 5.9, 11.2]; stratified HR 0.78 [0.63–0.97], p=0·028 (Figure 2) (20).

7.1.5 Efficacy – results per OS rates at 6, 12, 18 and 24 months for the ITT population

At 6 months the OS rate was 64% (95% CI: 58.6, 69.5) in the atezolizumab group compared with 58% (95% CI: 49.4, 65.7) in the chemotherapy group, with a difference of

6.5% (95% CI: -3.3, 16.3). The OS rate at 12 months was 44% (95% CI: 37.9, 49.4) in the atezolizumab group compared with 39% (95% CI: 30.5, 46.7) in the chemotherapy group, with a difference of 5.1% (95% CI: -4.9, 15.0). At 18 months the OS rate was 31% (95% CI: 26.0, 36.8) in the atezolizumab group compared with 24% (95% CI: 16.8, 31.2) in the chemotherapy group, with a difference of 7.4% (95% CI: -1.6, 16.5). At the time point the OS rates at 24 months were 24% (95% CI: 19.3, 29.4) in the atezolizumab group and 12% (95% CI: 6.7, 18.0) in the chemotherapy group, with a difference of 11.9% (95% CI: 4.4, 19.5) (Table 13) (20).

7.1.6 Efficacy – results per Investigator-assessed PFS for the ITT population

Median PFS was 4.2 months (95% CI: 3.7, 5.5) in the atezolizumab group compared with 4.0 months (95% CI: 2.9, 5.4) in the chemotherapy group (stratified HR 0.87 [0.70–1.07]), with numerically improved PFS rates with atezolizumab compared with chemotherapy at the 12-month (20% vs 14%) and 24-month landmarks (9% vs 2%) (Table 13) (20).

7.1.7 Efficacy – results per OS and investigator-assessed PFS in patients with PD-L1 expressing tumours as identified by the SP263 immunohistochemistry assay

For subgroup analyses across ECOG PS subgroups, the unstratified OS HR was 0.64 (95% CI: 0.36, 1.13) for ECOG PS 0–1, 0.86 (95% CI: 0.67, 1.10) for ECOG PS 2, and 0.74 (95% CI: 0.35, 1.57) for ECOG PS 3. Across histology types, the unstratified OS HR was 0.77 (95% CI: 0.58, 1.03) for non-squamous and 0.80 (95% CI: 0.58, 1.12) for squamous histology. The unstratified HR across PD-L1 expression levels (SP263 assay) was 0.81 (95% CI: 0.58, 1.11) in the PD-L1–negative subgroup, 0.84 (95% CI: 0.62, 1.15) in the PD-L1–positive subgroup, 0.84 (95% CI: 0.57, 1.22) in the PD-L1–low subgroup, 0.87 (95% CI: 0.50, 1.52) in the PD-L1–high subgroup, and 0.49 (95% CI: 0.21, 1.14) in the PD-L1–unknown group (Figure 4 and Figure 5) (20).

The unstratified PFS HRs across PD-L1 expression subgroups (SP263 assay) were 0.90 (95% CI: 0.66, 1.24) in the PD-L1–negative group, 0.83 (95% CI: 0.62, 1.12) in the PD-L1–positive group, 1.01 (95% CI: 0.69, 1.45) in the PD-L1–low group, and 0.64 (95% CI: 0.38–1.08) in the PD-L1–high group (20).

7.1.8 Efficacy – results per ORR and DoR using RECIST 1.1.

In the atezolizumab group, 51 (17%) of 302 patients (95% CI: 12.8, 21.6) had an objective response compared with 12 (8%) of 151 patients (95% CI: 4.2, 13.5) in the chemotherapy group . Median DoR was 14.0 months (95% CI: 8.1, 20.3) in the atezolizumab group compared with 7.8 months (95% CI: 4.8, 9·7) in the chemotherapy group (Table 13) (20).

8. Modelling of efficacy in the health economic analysis

N/A

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

N/A

8.1.1 Extrapolation of efficacy data

N/A

8.1.1.1 Extrapolation of [effect measure 1]

N/A

Table 14 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	N/A
Model	N/A
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	N/A
Function with best BIC fit	N/A
Function with best visual fit	N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	N/A

Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.1.2 Extrapolation of [effect measure 2]

N/A

8.1.2 Calculation of transition probabilities

N/A

Table 15 Transitions in the health economic model

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

8.2 Presentation of efficacy data from [additional documentation]

N/A

8.3 Modelling effects of subsequent treatments

N/A

8.4 Other assumptions regarding efficacy in the model

N/A

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

N/A

Table 16 Estimates in the model

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

Table 17 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

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

9. Safety

9.1 Safety data from the clinical documentation

The safety-evaluable population was defined as all randomized patients who received at least one dose of atezolizumab or chemotherapy. This population included 300 patients in the atezolizumab arm and 147 patients in the chemotherapy arm. The median treatment duration was 3.5 months (0.7–9.2) for atezolizumab, 2.3 months (1.1–3.4) for gemcitabine, and 1.8 months (1.0–3.8) for vinorelbine. The median number of treatment cycles was 6.0 (2.0–14.0) for atezolizumab, 4.0 (2.0–5.0) for gemcitabine, and 3.0 (2.0–6.0) for vinorelbine (20).

Follow-up data capture, including subsequent anticancer therapies, continued for each patient until death, withdrawal of consent, loss to follow up, or study termination by Sponsor, whichever occurred first (31). All serious AEs and AESIs was recorded during the trial and for up to 90 days after the last dose of study treatment or initiation of new anticancer therapy, whichever occurred first. All other AEs was recorded during the trial and

for up to 30 days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurred first (31).

Table 18 provides an overview of safety events started on or after first dose of study drug. Data are based on the period up until CCOD of April 30, 2022 (20). Differences between the two treatment arms in IPSOS were requested from the global study team. However, these differences were not calculated for the safety evaluation – hence not available.

Table 18 Overview of safety events started on or after first dose of study drug. Enrollment between September 11, 2017, and September 23, 2019. CCOD April 30, 2022 (20, 23).

	Atezolizumab (N=300) (20, 23)	Chemotherapy (N=147) (20, 23)	Difference, % (95 % CI)
[redacted]			NR
Number and proportion of patients with ≥1 adverse events, n (%)[a]	275 (92%)	143 (97%)	NR
Number of serious adverse events, n	NR	NR	NR
Number and proportion of patients with ≥ 1 serious adverse events, n (%)	146 (49%)	53 (36%)	NR
Number of CTCAE grade ≥ 3 events, n	NR	NR	NR
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events, n (%)[b]	171 (57%)	84 (57%)	NR
Number of adverse reactions, n	NR	NR	NR
Number and proportion of patients with ≥ 1 adverse reactions, n (%)[c]	171 (57%)	118 (80%)	NR
Number and proportion of patients who had a dose reduction, n (%)[d]	96 (32%)	71 (48%)	NR

Number and proportion of patients who discontinue treatment regardless of reason, n (%)	285 (95%)	147 (100%)	NR
Number and proportion of patients who discontinue treatment due to adverse events, n (%)[e]	39 (13%)	20 (14%)	NR

The median treatment duration was 3.5 months (0.7–9.2) for atezolizumab, 2.3 months (1.1–3.4) for gemcitabine, and 1.8 months (1.0–3.8) for vinorelbine (CCOD April 30, 2022). NR – Not reported

[a] All grade adverse events.

[b] This is not reported, however grade 3-4 and grade 5 are combined.

[c] All-grade adverse events treatment-related.

[d] Adverse events leading to modification or interruption of study drug.

[e] Adverse events leading to discontinuation of study drug.

The safety-evaluable population included 447 patients with 300 patients in the atezolizumab arm and 147 patients in the chemotherapy arm. All grade AEs occurred in 275 (92%) of 300 patients receiving atezolizumab and 143 (97%) of 147 patients receiving chemotherapy (Table 18).

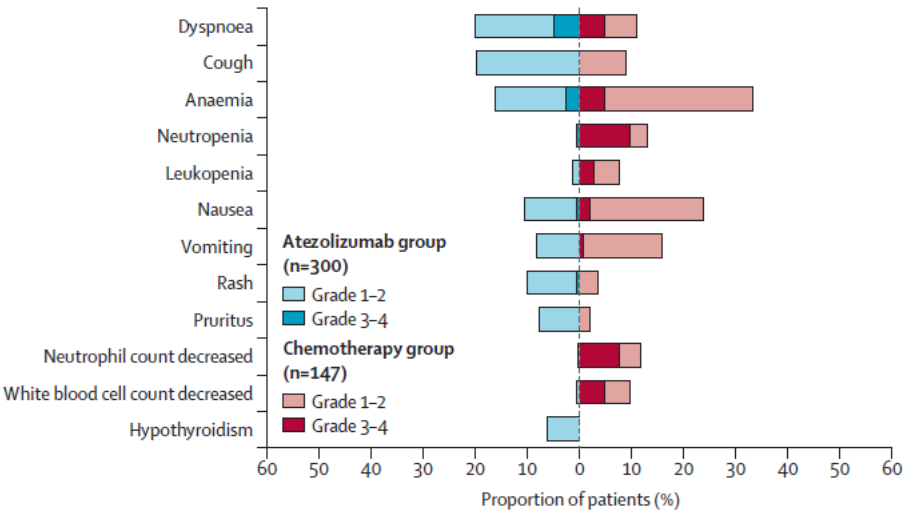

Figure 6 All grade adverse events that differed by 5% or more between treatment groups (20).

Of the all grade AEs that differed by 5% or more between treatment groups in the safety-evaluable population (Figure 6), the most common in the atezolizumab group were (23):

[redacted]

In the chemotherapy group, the most common were:

- [redacted]
- [redacted]

In the atezolizumab group, grade 3–4 AEs occurred in 136 (45%) patients and deaths occurred in 35 (12%) patients. In the chemotherapy arm, grade 3–4 AEs occurred in 71 (48%) patients and deaths occurred in 13 (9%) patients (20).

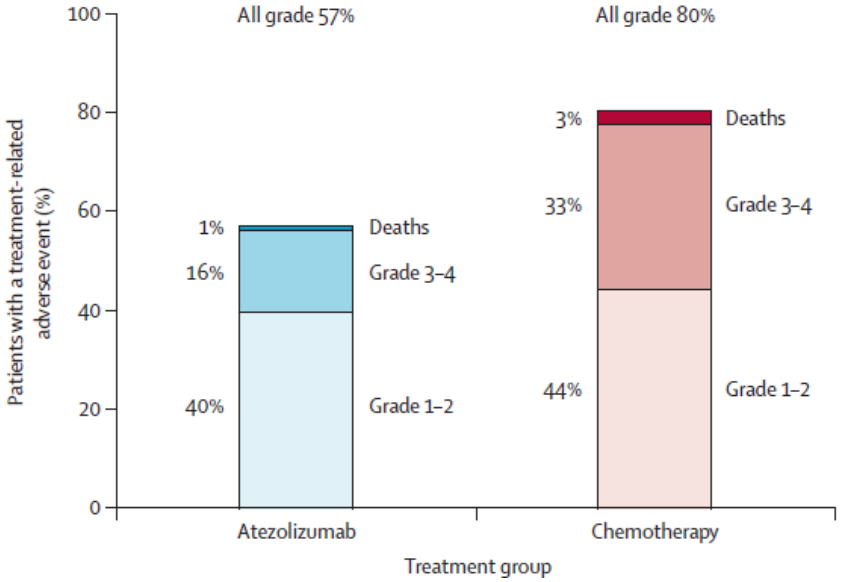

Figure 7 Proportions of patients having a treatment-related adverse event, by grade (20).

In the atezolizumab arm, treatment-related AEs occurred in 171 (57%) patients and were grade 3-4 in 49 (16%) patients. Treatment-related deaths occurred in 3 (1%) patients (Figure 7) and were due to acute left ventricular failure, immune-mediated hepatitis, and myasthenia gravis (1 patient per event) (20). In the chemotherapy arm, treatment-related AEs occurred in 118 (80%) patients and were grade 3–4 in (33%) 49 patients. Treatment-related deaths occurred in 4 (3%) patients (Figure 7) and were due to sepsis (2 patients), pneumonia (1 patient), and febrile neutropenia (1 patient) (20).

Serious Adverse Events (SAE)

[redacted]

Table 19 Serious adverse events in the Safety-evaluable population with an incidence rate of at least 5% in any treatment arm. started on or after first dose of study drug. Enrollment between September 11, 2017, and September 23, 2019. CCOD April 30, 2022 (20).

Adverse events	Atezolizumab (N=300) (23)		Chemotherapy (N=147) (23)	
	Number of patients with adverse events*	Number of adverse events*	Number of patients with adverse events*	Number of adverse events*
[redacted]				NR

The median treatment duration was 3.5 months (0.7–9.2) for atezolizumab, 2.3 months (1.1–3.4) for gemcitabine, and 1.8 months (1.0–3.8) for vinorelbine. NR – Not Reported.
*All counts represent patients. Multiple occurrences of the same AE in one individual are counted once.

SAEs occurred in 146 (49%) patients in the atezolizumab group and 53 (36%) patients in the chemotherapy group (Table 18). SAEs were related to treatment in 35 (12%) patients in the atezolizumab group and 23 (16%) patients in the chemotherapy group. Treatment discontinuation due to AEs occurred in 39 (13%) patients receiving atezolizumab and 20 (14%) patients receiving chemotherapy (Table 18) (20).

The proportion of patients with at least 1 SAE was higher in the atezolizumab arm with 146 (49%) patients compared to 53 (36%) patients in the chemotherapy arm (Table 18). This could be reflective of the longer exposure to treatment in the atezolizumab arm compared with the chemotherapy arm and the higher percentage of patients in the atezolizumab arm who continued study treatment beyond 12 months (23).

Adverse Events of Special Interest (AESI)
Identified risks for use of atezolizumab in the IPSOS study are AESIs for which there is scientific evidence of a causal association between the risk and treatment. AESIs that are considered identified risks for atezolizumab in the IPSOS study are presented in Table 20. These AESIs represent risks with an established or potential causal association of atezolizumab use (23).

Table 20 Adverse events of special interest in the safety-evaluable population (20).

	Atezolizumab (n=300) (20)	Chemotherapy (n=147) (20)
AESI, n (%)	**102 (34%)**	**27 (18%)**
Immune-mediated rash, n (%)	45 (15%)	11 (7%)
Immune-mediated hepatitis (diagnosis and lab abnormalities), n (%)	32 (11%)	9 (6%)
Immune-mediated hepatitis (lab abnormalities), n (%)	27 (9%)	8 (5%)

Immune-mediated hepatitis (diagnosis), n (%)	7 (2%)	1 (1%)
Immune-mediated hypothyroidism, n (%)	27 (9%)	1 (1%)
Immune-mediated pneumonitis, n (%)	13 (4%)	3 (2%)
Immune-mediated hyperthyroidism, n (%)	7 (2%)	3 (2%)
Immune-mediated diabetes mellitus, n (%)	4 (1%)	0
Immune-mediated colitis, n (%)	3 (1%)	0
Immune-mediated pancreatitis, n (%)	3 (1%)	0
Infusion-related reactions, n (%)	2 (1%)	0
Immune-mediated adrenal insufficiency, n (%)	1 (<1%)	0
Immune-mediated myasthenia gravis	1 (<1%)	0
Immune-mediated myocarditis	1 (<1%)	0
Immune-mediated nephritis	0	1 (1%)

AESI – Adverse event of special interest.

Overall, the proportion of patients in the safety-evaluable population who experienced AESIs were 34% in the atezolizumab arm and 18% in the chemotherapy arm (Table 20). [redacted]

[redacted] Treatment-related deaths of special interest were due to immune-mediated pneumonitis (1 patient), immune-mediated hepatitis (1 patient, diagnosis), and immune-mediated myasthenia gravis (1 patient) (20, 23). [redacted]

AESI occurred in 27 (18%) patients in the safety-evaluable population in the chemotherapy arm. The most common were rash observed in 11 (7%) patients and hepatitis (diagnosis and laboratory abnormalities) observed in 9 (6%) patients (Table 20). AESI were grade 3–4 in 3 (2%) patients, and no patient in the chemotherapy group had a treatment-related death (20). [redacted]

No new or unexpected AESI were identified with atezolizumab, and treatment-related grade three or four AEs and treatment-related deaths occurred in a smaller proportion of patients receiving atezolizumab compared with chemotherapy. Furthermore, rates of all-grade AESIs in the atezolizumab group were consistent with previous atezolizumab monotherapy trials in patients with NSCLC and ECOG PS 0–1 (35, 36). These data suggest that atezolizumab was well tolerated in this poor-prognosis population, despite a longer safety collection window for atezolizumab versus chemotherapy. The higher incidence of AESIs observed in the atezolizumab arm compared to the chemotherapy arm may be attributable to differences in their mechanisms of action, reflecting the immune-modulating properties of atezolizumab in contrast to the cytotoxic nature of chemotherapy.

The safety profile of atezolizumab is well-characterized across multiple indications, and findings from the IPSOS study indicate a safety profile similar to that observed in other NSCLC studies with comparable patient populations (PD-L1 expression level, ECOG PS score, and histology subgroups), with no new safety signals identified.

Table 21 Adverse events used in the health economic model

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

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

N/A

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

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

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

The patient-reported outcome (PRO) objective was to evaluate and compare PROs of lung cancer symptoms, patient functioning, and health-related quality of life (HRQoL) between treatment arms as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-life Questionnaire Core 30 (QLQ-C30) and its Lung Cancer Module (QLQ-LC13) (20, 23, 31) (Table 23).

Table 23 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EORTC QLQ-C30	IPSOS (MO29872) (Aaronson et al. 1993)	Assessed PROs of lung cancer-related symptoms (i.e., cough, dyspnea, fatigue, pain in chest; pain in arm/shoulder), patient functioning, and HRQoL
EORTC QLQ-LC13	IPSOS (MO29872) (Bergman et al. 1994)	Assessed PROs of lung cancer-related symptoms (i.e., cough, dyspnea, fatigue, pain in chest; pain in arm/shoulder), patient functioning, and HRQoL
EQ-5D-5L	IPSOS (MO29872)	The EQ-5D-5L was utilized in this study to generate utility scores for potential use in economic models for reimbursement

10.1 Presentation of the health-related quality of life [make a subsection for each of the applied HRQoL instruments]

10.1.1 Study design and measuring instrument

PRO data were collected with the EORTC QLQ-C30, the EORTC QLQ-LC13, and EQ-5D-5L to more fully characterize the clinical profile of atezolizumab.

The EORTC QLQ-C30 is a validated and reliable self-report measure consisting of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), 3 symptom scales (fatigue, nausea and vomiting, pain), global health/quality of life, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) (23, 37, 38).

The EORTC QLQ-LC13 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 (23).

The EQ-5D-5L is a generic, preference-based health utility measure with questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that is used to build a composite of the patient's health status (23).

PROs analyses were performed in the ITT population. PROs of lung cancer-related symptoms and treatment impact on functioning and HRQoL (as measured by the EORTC QLQ-C30 and EORTC QLQ-LC13) were evaluated as secondary efficacy endpoints (23).

The PRO measures were the following (31):

• Change from baseline in PROs of lung cancer symptoms, patient functioning, HRQoL as assessed by EORTC QLQ-C30 and its supplementary Lung Cancer module (LC13)

• Time to deterioration (TTD) in patient-reported lung cancer symptoms of cough, dyspnea (single-item and multi-item subscales), chest pain, arm/shoulder pain, or fatigue using EORTC QLQ-C30 and QLQ-LC13

It is important to understand the impact of delay in disease progression in lung cancer and that it is specifically meaningful to lung cancer patients with a low performance status (31). In the treatment of lung cancer, it is generally important to both increase survival and palliate symptoms because disease symptoms have negative impacts on HRQoL (39-41).

Chest pain, dyspnea, and cough have been regarded as the most frequent and clinically relevant disease-related symptoms experienced by patients with NSCLC. Studies has demonstrated that longer TTD in the pain, dyspnea, and cough scales of the EORTC QLQ-C30 and QLQ-LC13 was consistent with superior PFS, OS, and quality-of-life benefits (37, 42-44).

10.1.2 Data collection

Summary statistics (mean, standard deviation, median, and range) of linear transformed scores were reported for all the items and subscales of the EORTC QLQ-C30 and the QLQ-LC13 according to the EORTC scoring manual guidelines. The proportion of patients showing clinically meaningful change in selected items and subscales at each assessment time point was calculated, with clinically meaningful defined as a change in symptoms/functioning (i.e., reduction or increase) from baseline to the threshold of 10 points or more (45). Completion rates were summarized at each time point by treatment arm. Only patients with a baseline assessment and at least one post-treatment assessment were included in the analyses (31).

Table 24 Pattern of missing data and completion for EORTC QLQ-C30 (23).

Time point	HRQoL population N		Missing N (%)		Expected to complete N		Completion N (%)	
	Number of patients at randomization		Number of patients for whom data is missing (% of patients at randomization)		Number of patients "at risk" at time point X		Number of patients who completed (% of patients expected to complete)	
	Atezolizumab	Chemotherapy	Atezolizumab	Chemotherapy	Atezolizumab	Chemotherapy	Atezolizumab	Chemotherapy

Table 25 Pattern of missing data and completion for EORTC QLQ-LC13 (16).

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is	Number of patients "at	Number of patients who completed (%

			missing (% of patients at randomization)		risk" at time point X		of patients expected to complete)	
	Atezolizumab	Chemotherapy	Atezolizumab	Chemotherapy	Atezolizumab	Chemotherapy	Atezolizumab	Chemotherapy

Table 26 Pattern of missing data and completion for EQ-5D-VAS (23).

Time point	HRQoL population N	Missing N (%)		Expected to complete N		Completion N (%)	
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)		Number of patients "at risk" at time point X		Number of patients who completed (% of patients expected to complete)	
	Atezolizumab	Chemotherapy	Atezolizumab	Chemotherapy	Atezolizumab	Chemotherapy	Atezolizumab	Chemotherapy

Completion rates were based on the number of patients that were known to be alive and progression-free at the respective time point. Completion rates were high at baseline for the EORTC QLQ-C30 (97.4% in both atezolizumab and chemotherapy arms), EORTC QLQ-LC13 (98.0% in the atezolizumab arm and 97.4% in the chemotherapy arm) and EQ-5D-VAS (97.4% in the atezolizumab arm and 92.7% in the chemotherapy arm). In the atezolizumab arm, the completion rate remained above 70% until Week 75. In the chemotherapy arm, the completion rate decreased to 55% at Week 48 (with a 46% completion rate at Week 36). Data were available for ≥10 patients in either treatment arm through week 48; therefore, change from baseline summaries are interpreted from weeks 0 to 48 (23).

10.1.3 HRQoL results

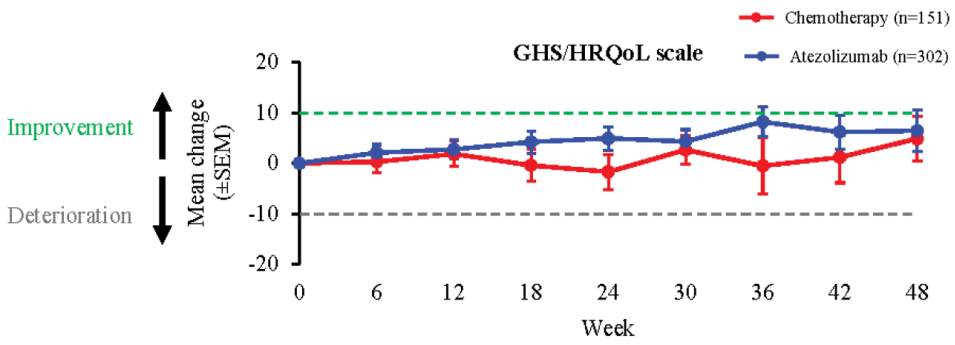

Figure 8 Change from baseline in health-related quality-of-life functioning scales by the EORTC QLQ-C30 symptom scale. Error bars represent SEM. EORTC-European Organisation for Research and Treatment of Cancer; GHS-global health status; HRQoL-health-related quality of life; QLQ-C30-Quality-of-Life Questionnaire Core 30; QLQ-LC13-Quality-of-Life Questionnaire, lung cancer module (20).

Table 27 HRQoL EORTC QLQ-C30 Functioning Domains and Global quality of life Scores in the ITT population (23).

	Atezolizumab		Chemotherapy		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
[redacted]					

For the patient-reported HRQoL and functioning scales as measured by EORTC QLQ-C30, both the atezolizumab and chemotherapy groups remained stable in physical functioning, emotional functioning and global health status (Figure 8 Change from baseline in health-related quality-of-life functioning scales by the EORTC QLQ-C30 symptom scale. Error bars represent SEM. EORTC-European Organisation for Research and Treatment of Cancer; GHS-global health status; HRQoL-health-related quality of life; QLQ-C30-Quality-of-Life Questionnaire Core 30; QLQ-LC13-Quality-of-Life Questionnaire, lung cancer module (20).Figure 8) (23). Global health status (GHS) is presented in Figure 8 Change from baseline in health-related quality-of-life functioning scales by the EORTC QLQ-C30 symptom scale. Error bars represent SEM. EORTC-European Organisation for Research and Treatment of Cancer; GHS-global health status; HRQoL-health-related quality of life; QLQ-C30-Quality-of-Life Questionnaire Core 30; QLQ-LC13-Quality-of-Life Questionnaire, lung cancer module (20).Figure 8 above, while the remaining functioning scales is presented in Appendix F. GHS is an index indicating the overall quality of life on a scale ranging from “very poor” overall health status to “excellent” overall health status, and can be utilized as a proxy for quality of life. The atezolizumab arm showed clinically meaningful improvements for appetite loss, constipation, dyspnoea (QLQ-LC13 only), cough, and pain in chest (Appendix F) (46). By contrast, the chemotherapy arm showed clinically meaningful deteriorations across several functioning domain such as role, social, and cognitive and symptoms such as appetite loss, peripheral neuropathy, alopecia, and pain in other parts (Appendix F). Clinically meaningful improvement was observed in the chemotherapy arm for insomnia and pain. For the symptom ‘pain in other parts’, clinically meaningful deterioration and improvement were observed at different timepoints in the chemotherapy arm. Maintenance of baseline health was observed in both arms for fatigue, nausea and vomiting, dyspnea (QLQ-C30), diarrhea, haemoptysis, sore mouth, dysphagia, pain in arm or shoulder, and financial difficulties (Appendix F) (23). Atezolizumab showed a benefit over chemotherapy for time-to-confirmed-deterioration in chest pain (QLQ-LC13; stratified HR 0.51 (95% CI 0.27, 0.97)) (Table 47) (20, 46).

Table 28 HRQoL 5Q-5D-5L: Your health today (VAS) in the ITT population (23).

	Atezolizumab		Chemotherapy		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
[redacted]					

The results indicate a tendency for the EQ-5D-VAS score to improve with atezolizumab compared to chemotherapy. However, this tendency is not statistically significant at any of the follow-up visits due to the sample size. Therefore, it is not possible to conclude whether atezolizumab improves the quality of life compared to chemotherapy.

The EQ-5D-VAS was included in the IPSOS study only as an exploratory measure and was not intended for presentation or publication. Thus, graphic illustrations have not been produced.

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

N/A

10.2.1 HSUV calculation

N/A

10.2.1.1 Mapping

N/A

10.2.2 Disutility calculation

N/A

10.2.3 HSUV results

N/A

Table 29 Overview of health state utility values [and disutilities]

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

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

N/A

10.3.1 Study design

N/A

10.3.2 Data collection

N/A

10.3.3 HRQoL Results

N/A

10.3.4 HSUV and disutility results

N/A

Table 30 Overview of health state utility values [and disutilities]

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

…				
[Disutilities]	N/A	N/A	N/A	N/A
…				

Table 31 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV A				
Study 1	N/A	N/A	N/A	N/A
Study 2	N/A	N/A	N/A	N/A
Study 3	N/A	N/A	N/A	N/A
HSUV B				
…	N/A	N/A	N/A	N/A
[Disutility A]				
…	N/A	N/A	N/A	N/A

11. Resource use and associated cost

N/A

11.1 Medicine costs - intervention and comparator

N/A

Table 32 Medicine costs used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
[Name of the intervention]	N/A	N/A	N/A	N/A

[Name of the comparator]	N/A	N/A	N/A	N/A

11.2 Medicine costs – co-administration

N/A

11.3 Administration costs

N/A

Table 33 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
[E.g. i.v. infusion, subcutaneous infusion]	N/A	N/A	N/A	N/A

11.4 Disease management costs

N/A

Table 34 Disease management costs used in the model

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

11.5 Costs associated with management of adverse events

N/A

Table 35 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
[Adverse event]	N/A	N/A
[Adverse event]	N/A	N/A

11.6 Subsequent treatment costs

N/A

Table 36 Medicine costs of subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
[Name of subsequent treatment]	N/A	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A	N/A
[Name of subsequent treatment]	N/A	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A	N/A

11.7 Patient costs

N/A

Table 37 Patient costs used in the model

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

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

N/A

12. Results

N/A

12.1 Base case overview

N/A

Table 38 Base case overview

Feature	Description
Comparator	N/A
Type of model	N/A
Time horizon	N/A
Treatment line	N/A

Measurement and valuation of health effects	N/A
Costs included	N/A
Dosage of medicine	N/A
Average time on treatment	N/A
Parametric function for PFS	N/A
Parametric function for OS	N/A
Inclusion of waste	N/A
Average time in model health state	N/A
Health state 1	
Health state 2	
Health state 3	
Death	

12.1.1 Base case results

N/A

Table 39 Base case results, discounted estimates

	[Intervention]	[Comparator]	Difference
Medicine costs	N/A	N/A	N/A
Medicine costs – co-administration	N/A	N/A	N/A
Administration	N/A	N/A	N/A
Disease management costs	N/A	N/A	N/A
Costs associated with management of adverse events	N/A	N/A	N/A
Subsequent treatment costs	N/A	N/A	N/A
Patient costs	N/A	N/A	N/A
Palliative care costs	N/A	N/A	N/A

Total costs	**N/A**	**N/A**	**N/A**
Life years gained (health state A)	N/A	N/A	N/A
Life years gained (health state B)	N/A	N/A	N/A
Total life years	**N/A**	**N/A**	**N/A**
QALYs (state A)	N/A	N/A	N/A
QALYs (state B)	N/A	N/A	N/A
QALYs (adverse reactions)	N/A	N/A	N/A
Total QALYs	**N/A**	**N/A**	**N/A**
Incremental costs per life year gained		**N/A**	
Incremental cost per QALY gained (ICER)		**N/A**	

12.2 Sensitivity analyses

N/A

12.2.1 Deterministic sensitivity analyses

N/A

Table 40 One-way sensitivity analyses results

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

12.2.2 Probabilistic sensitivity analyses

N/A

13. Budget impact analysis

N/A

Number of patients (including assumptions of market share)

N/A

Table 41 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
[Name of intervention]	N/A	N/A	N/A	N/A	N/A
[Name of comparator]	N/A	N/A	N/A	N/A	N/A
			Non-recommendation		
[Name of intervention]	N/A	N/A	N/A	N/A	N/A
[Name of comparator]	N/A	N/A	N/A	N/A	N/A

Budget impact

Table 42 Expected budget impact of recommending the medicine for the indication

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

14. List of experts

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Appendix A. Main characteristics of studies included

Table 43 Main characteristic of studies included

Trial name: IPSOS	**NCT number: NCT03191786**
Objective	This study will evaluate the efficacy and safety of atezolizumab compared with single agent chemotherapy with respect to antitumor effects in patients with treatment-naïve locally advanced or metastatic non-small cell lung cancer (NSCLC) who are deemed unsuitable for any platinum-doublet chemotherapy.
Publications – title, author, journal, year	First-line atezolizumab monotherapy versus single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen (IPSOS): a phase 3, global, multicentre, open-label, randomised controlled study; Lee et al; The Lancet; 2023
Study type and design	a phase 3, global, multicentre, open-label, randomised controlled study the study is completed
Sample size (n)	453
Main inclusion criteria	• Histologically or cytologically confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC as per the American Joint Committee on Cancer (AJCC) 7th edition • No sensitizing epidermal growth factor receptor (EGFR) mutation (L858R or exon 19 deletions) or anaplastic lymphoma kinase (ALK) fusion oncogene detected • No prior systemic treatment for advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC as per the AJCC 7th edition • Life expectancy greater than or equal to (>/=) 8 week • Deemed unsuitable by the investigator for any platinum-doublet chemotherapy due to poor performance status (ECOG performance status of 2-3). However, participants >= 70 years of age who have an ECOG PS of 0 or 1 may be included due to: a) substantial comorbidities; b) contraindication(s) for any platinum-doublet chemotherapy • Representative formalin-fixed paraffin-embedded (FPPE) tumor tissue block obtained during course of disease (archival tissue) or at screening • Participants with treated, asymptomatic central nervous system (CNS) metastases are eligible, provided they meet all of the following criteria: Measurable disease outside CNS; Only supratentorial and cerebellar metastases allowed; No ongoing requirement for corticosteroids as therapy for CNS disease;

	No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomization; No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study • Adequate hematologic and end organ function • Female participants of childbearing potential randomized to the atezolizumab treatment arm agree to use protocol defined methods of contraception
Main exclusion criteria	<u>Cancer-Specific Exclusion Criteria:</u> • Participants younger than 70 years who have an ECOG performance status of 0 or 1 • Active or untreated CNS metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation of the brain during screening and prior radiographic assessments • Uncontrolled tumor-related pain • Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently) • Uncontrolled or symptomatic hyerpcalcemia (ionized calcium > 1.5 mmol/L or calcium >12 mg/dL or corrected serum calcium >ULN) • History of other malignancy within 5 years prior to screening, with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome • National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 (v4.0) Grade 3 or higher toxicities due to any prior therapy (example [e.g.], radiotherapy) (excluding alopecia), which have not shown improvement and are strictly considered to interfere with current study medication • Participants who have received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from randomization since the last chemotherapy, radiotherapy, or chemoradiotherapy <u>General Medical Exclusion Criteria:</u> • History of autoimmune disease except autoimmune-related hypothyroidism and controlled Type I diabetes mellitus • History of idiopathic pulmonary fibrosis (IPF), organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced

pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis

- Known positivity for human immunodeficiency virus (HIV)
- Known active hepatitis B or hepatitis C
- Active tuberculosis
- Severe infections within 4 weeks prior to randomization
- Significant cardiovascular disease, such as New York Heart Association (NYHA) cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina
- Major surgical procedure other than for diagnosis within 4 weeks prior to randomization or anticipation of need for a major surgical procedure during the course of the study
- Prior allogeneic bone marrow transplantation or solid organ transplant
- Participants with an illness or condition that may interfere with capacity or compliance with the study protocol, as per investigator's judgment
- Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days prior to randomization

Exclusion Criteria Related to Atezolizumab:

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- Oral or IV antibiotic treatment
- Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation that such a live attenuated vaccine will be required during the study
- Prior treatment with cluster of differentiation 137 (CD137) agonists or immune checkpoint blockade therapies, anti-programmed death-1 (anti-PD-1), and anti-PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to randomization
- Treatment with systemic corticosteroids or other immunosuppressive medications
- Participants not willing to stop treatment with traditional herbal medicines

	Exclusion Criteria Related to Chemotherapy: • Known sensitivity and contraindications to the 2 comparative chemotherapy agents (that is [i.e.] vinorelbine, oral or IV, and gemcitabine, IV)
Intervention	Tecentriq (atezolizumab); fixed dose of 1200 mg; Atezolizumab will be administered via IV infusion once every three weeks (QW3). 302 patients was assigned to the atezolizumab arm.
Comparator(s)	Single-agent chemotherapy (gemcitabine or vinorelbine) based on investigator's choice will be administered per relevant local guidelines and SmPC management. Doses and dose modifications for the selected single agent chemotherapy should be made per relevant local guidelines and SmPC management. 151 patients was assigned to the chemotherapy arm. 63 patients received gemcitabine and 84 received vinorelbine.
Follow-up time	Median follow-up was 41.0 months (Interquartile range 36.7–47.8)
Is the study used in the health economic model?	No, as no health economic assessment is need for this application
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** **Efficacy Objectives** Primary Efficacy Objective: The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab compared with single agent chemotherapy in patients with treatment-naïve locally advanced or metastatic NSCLC who are deemed unsuitable for any platinum-doublet chemotherapy, as measured by overall survival (OS). Secondary Efficacy Objectives The secondary efficacy objectives for this study are: • To evaluate the efficacy of atezolizumab compared with single agent chemotherapy as measured by OS rates at 6, 12, 18 and 24 months • To evaluate the efficacy of atezolizumab compared with single agent chemotherapy with respect to antitumor effects as measured by investigator-assessed ORR using RECIST v1.1 "Use of this document is governed by the terms of use on the first page of this document." Atezolizumab—F. Hoffmann-La Roche Ltd 33/Protocol MO29872, Version 7 • To evaluate the efficacy of atezolizumab compared with single agent chemotherapy with respect to antitumor effects as measured by investigator-assessed progression-free survival (PFS) using RECIST v1.1 • To evaluate the efficacy of atezolizumab compared with single

agent chemotherapy with respect to antitumor effects as measured by investigator-assessed duration of response (DoR) using RECIST v1.1

- To evaluate the efficacy (OS and investigator-assessed PFS using RECIST v1.1) of atezolizumab compared with single agent chemotherapy in patients with PD-L1 expression defined by the PD-L1 SP263 immunohistochemistry (IHC) assay

Safety Objective

The safety objective for this study is:

- To evaluate the safety and tolerability of atezolizumab compared with single agent chemotherapy

Patient-reported Outcome Objectives

The patient-reported outcome (PRO) objective for this study is:

- To evaluate and compare PROs of lung cancer symptoms, patient functioning, and health-related quality of life (HRQoL) between treatment arms as measured by the European Organisation for Research and treatment of Cancer (EORTC) Quality-of-life Questionnaire Core 30 (QLQ C30) and its Lung Cancer Module (QLQ LC13)

Other endpoints:

The exploratory objectives for this study are:

- To evaluate the efficacy of atezolizumab compared with single agent chemotherapy with respect to antitumor effects as measured by investigator-assessed ORR, PFS and DoR according to modified RECIST (immune-mediated response criteria; imRC)
- To evaluate and compare investigator-assessed disease control rates (DCR) between the two treatment arms using RECIST v1.1
- To evaluate the relationship between the main efficacy endpoints and tumor tissue programmed death-ligand 1 (PD-L1) expression
- To evaluate the relationship between the main efficacy endpoints and exploratory biomarkers in tumor tissue and plasma
- To evaluate the relationship between the main efficacy endpoints and the expression of immune markers in peripheral blood mononuclear cells (PBMCs)
- To generate utility scores for use in economic models for reimbursement by collecting patient's health status data using the EuroQoL-5 Dimensions 5-level (EQ-5D-5L) questionnaire

Method of analysis	The primary efficacy endpoint was the comparison of overall survival between the two groups in the intention-to-treat (ITT) population. Secondary efficacy endpoints included overall survival rates at 6, 12, 18, and 24 months; investigator-assessed progression-free survival; overall

	survival and investigator-assessed progression-free survival in patients with PD-L1 expressing tumours as identified by the SP263 immunohistochemistry assay; and objective response rate and duration of response using RECIST 1.1. Other endpoints included patient-reported health-related QoL outcomes and safety. We used Kaplan-meier method to estimates rates of OS for each treatment group. Safety assessments included the incidence, nature, and severity of adverse events and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Adverse events of special interest were recorded and represent risks, selected based on the mechanism of action of atezolizumab. Interim and final analysis was planed for the primary endpoint OS for the ITT population. Efficacy analyses were conducted in the ITT population. The HRs for overall survival and progression-free survival were estimated by a stratified Cox regression model, including two-sided 95% CIs. Overall survival rates were estimated using Kaplan-Meier methodology for each treatment group. The same calculations detailed for the overall survival analysis were used for the duration of response, but comparisons made between treatment groups were for descriptive purposes only. An estimate of objective response rate and its 95% CI was calculated using the Clopper-Pearson method for each treatment group. CIs for the difference in objective response rate between the two groups were determined using the normal approximation to the binomial distribution. The objective response rate was compared between the two groups using a $\chi 2$ test. Time-to-confirmed-deterioration was also based on published meaningful change metrics and summarised using Kaplan-Meier methodology for each group, and comparisons between treatment groups were performed using the stratified log-rank test. Safety analyses were conducted in the safety-evaluable population, which included all randomised patients who received any amount of atezolizumab or chemotherapy
Subgroup analyses	Subgroups included PD-L1 expression level, ECOG PS score, and histology all was unstratified and was done for OS and PFS OS is described by PD-L1 subgroups. Kaplan-Meier OS estimates in the intention-to-treat population for the PD-L1–negative subgroup and PD-L1–positive subgroup, as assessed by the SP263 immunohistochemistry assay. Unstratified HRs are reported. Predefined PD-L1 cut-offs were PD-L1–negative: tumour cells less than 1%; PD-L1–positive: tumour cells 1% or more; PD-L1–low: tumour cells 1–49%; PD-L1–high: tumour cells 50% or more; or unknown. PFS is described in key patient subgroups. HR was stratified for all patients and unstratified for all subgroup analyses. Characteristics are described in supplementary figure 2 in lee et al. (46).
Other relevant information	N/A

Appendix B. Efficacy results per study

Results per study

Table 44 Results per study

Results of IPSOS (MO29872)											
				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 overall survival	Atezolizumab	302	10.3 (9.4-11.9) months	N/A	N/A	N/A	HR: 0.78	0.63-0.97	0.028	The OS was assessed using the Kaplan-Meier (KM) method to estimate survival curves for both treatment arms. The log-rank test was employed to compare OS between the groups, and a Cox proportional hazards model was used to calculate the HR and 95% confidence intervals (CIs), stratified by factors such as histology, brain metastasis status, and PD-L1 expression level.	(20, 46)
	Chemotherapy	151	9.2 (5.9-11.2) months								
Overall survival 6-month rate	Atezolizumab	302	64% (58.6-69.5)	N/A	N/A	N/A	6.5%	-3.3-16.3	N/A	The OS was assessed using the Kaplan-Meier (KM) method to estimate survival curves for both treatment arms. The log-rank test was employed to compare OS between the groups, and a Cox proportional hazards model was used to	(20, 46)
	Chemotherapy	151	58% (49.4-65.7)								

Results of IPSOS (MO29872)											
				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		
										calculate the HR and 95% confidence intervals (CIs), stratified by factors such as histology, brain metastasis status, and PD-L1 expression level.	
Overall survival 12-month rate	Atezolizumab	302	44% (37.9-49.4)	N/A	N/A	N/A	5.1%	-4.9-15.0	N/A	The OS was assessed using the Kaplan-Meier (KM) method to estimate survival curves for both treatment arms. The log-rank test was employed to compare OS between the groups, and a Cox proportional hazards model was used to calculate the HR and 95% confidence intervals (CIs), stratified by factors such as histology, brain metastasis status, and PD-L1 expression level.	(20, 46)
	Chemotherapy	151	39% (30.5-46.7)								
Overall survival 18-month rate	Atezolizumab	302	31% (26.0-36.8)	N/A	N/A	N/A	7.4%	-1.6-16.5	N/A	The OS was assessed using the Kaplan-Meier (KM) method to estimate survival curves for both treatment arms. The log-rank test was employed to compare OS between the groups, and a Cox proportional hazards model was used to calculate the HR and 95% confidence intervals (CIs), stratified by factors such as	(20, 46)
	Chemotherapy	151	24% (16.8-31.2)								

Results of IPSOS (MO29872)											
				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		
										histology, brain metastasis status, and PD-L1 expression level.	
Overall survival 24-month rate	Atezolizumab	302	24% (19.3-29.4)	N/A	N/A	N/A	11.9%	4.4-19.5	N/A	The OS was assessed using the Kaplan-Meier (KM) method to estimate survival curves for both treatment arms. The log-rank test was employed to compare OS between the groups, and a Cox proportional hazards model was used to calculate the HR and 95% confidence intervals (CIs), stratified by factors such as histology, brain metastasis status, and PD-L1 expression level.	(20, 46)
	Chemotherapy	151	12% (6.7-18.0)								
Median Progression-free survival, months	Atezolizumab	302	4.2 (3.7-5.5)	N/A	N/A	N/A	HR: 0.87	0.70-1.07	N/A	PFS was defined as the time (in months) between the date of randomization and the date of first documented disease progression or death, whichever occured first. Disease progression was determined based on investigator assessment using RECIST v1.1. Patients who had not experienced disease progression or death at the time of analysis	(20, 46)
	Chemotherapy	151	4.0 (2.9-5.4)								

Results of IPSOS (MO29872)											
				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		
										were be censored at the time of last tumor assessment. Patients with no post-baseline tumor assessment were censored at the randomization date plus 1 day.	
Progression-free survival 12-month rate	Atezolizumab	302	20 (15.0-24.3)	N/A	N/A	N/A	5.5%	-2.0-13.0	N/A	PFS was defined as the time (in months) between the date of randomization and the date of first documented disease progression or death, whichever occured first. Disease progression was determined based on investigator assessment using RECIST v1.1. Patients who had not experienced disease progression or death at the time of analysis were be censored at the time of last tumor assessment. Patients with no post-baseline tumor assessment were censored at the randomization date plus 1 day.	(20, 23, 46)
	Chemotherapy	151	14 (8.3-20.0)								
Progression-free survival	Atezolizumab	302	9 (5.5-12.2)	N/A	N/A	N/A	7.3%	3.3-11.3	N/A	PFS was defined as the time (in months) between the date of randomization and the date of first documented disease	(20, 23, 46)

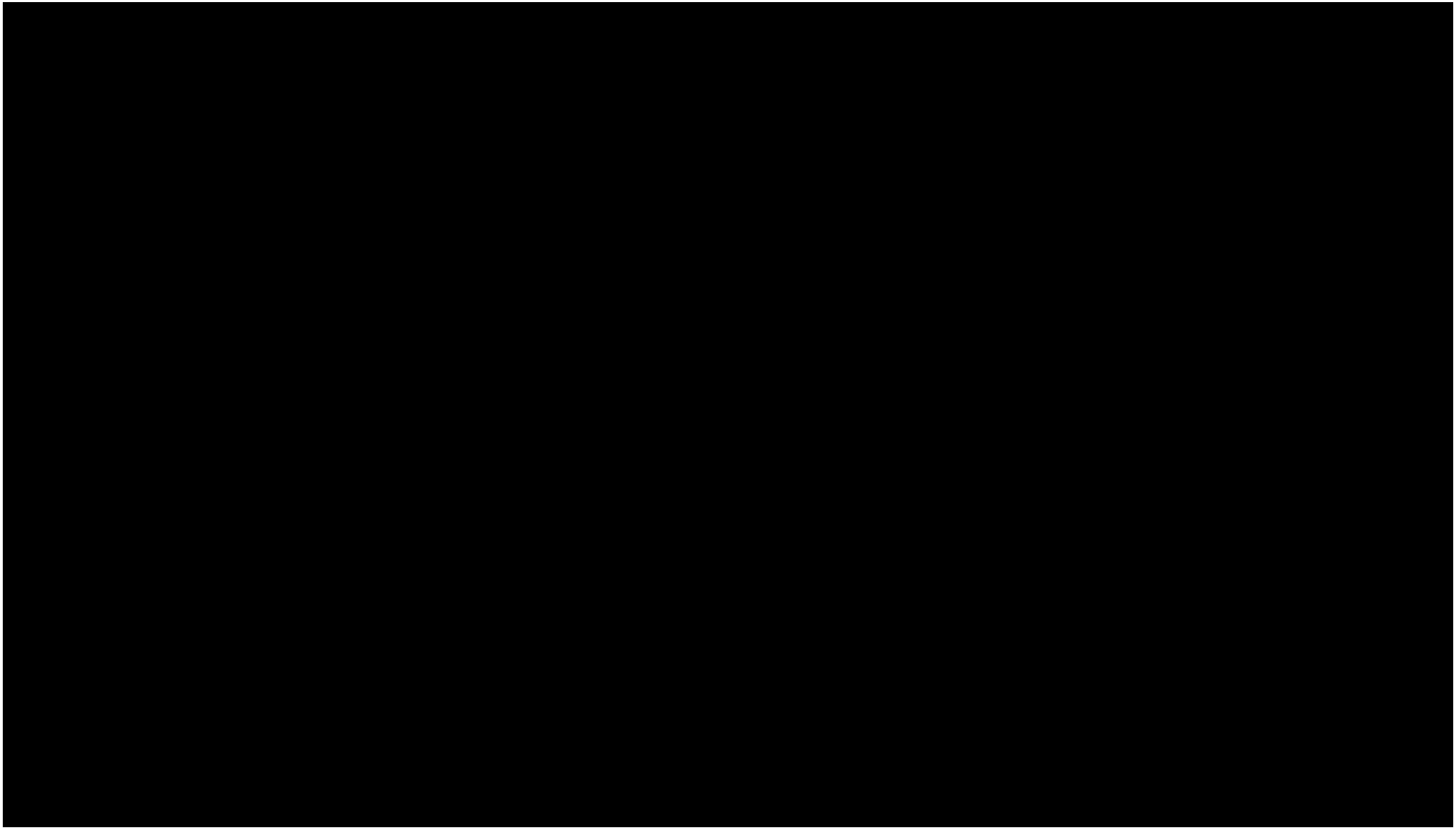
Results of IPSOS (MO29872)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
24-month rate	Chemotherapy	151	2 (0.0-3.7)							progression or death, whichever occured first. Disease progression was determined based on investigator assessment using RECIST v1.1. Patients who had not experienced disease progression or death at the time of analysis were be censored at the time of last tumor assessment. Patients with no post-baseline tumor assessment were censored at the randomization date plus 1 day.	
Objective response	Atezolizumab	302	51 (17%; 12.8-21.6)	N/A	N/A	N/A	8.9%	2.4-15.5	N/A	The analysis population for ORR was all randomized patients that had a measurable disease at baseline. An estimate of ORR and its 95% CI was calculated using the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs between the two arms was determined using the normal approximation to the binomial distribution	(20, 23, 46)
	Chemotherapy	151	12 (8%; 4.2-13.5)								

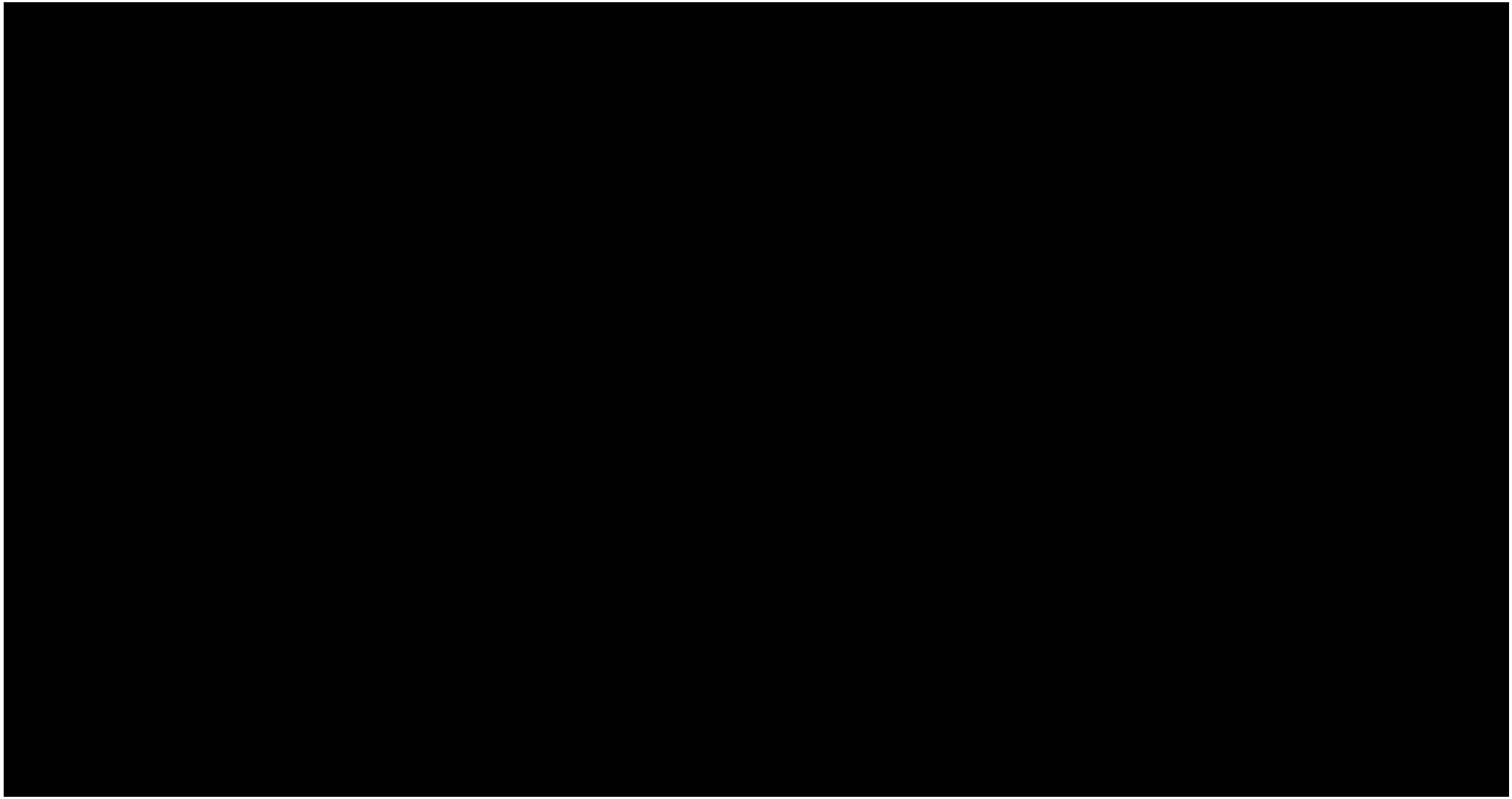
Results of IPSOS (MO29872)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Complete response	Atezolizumab	302	4 (1%)	N/A	N/A	N/A	1%	N/A	N/A	The analysis population for ORR was all randomized patients that had a measurable disease at baseline. An estimate of ORR and its 95% CI was calculated using the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs between the two arms was determined using the normal approximation to the binomial distribution	(20, 46)
	Chemotherapy	151	0								
Partial response	Atezolizumab	302	47 (16%)	N/A	N/A	N/A	8%	N/A	N/A	The analysis population for ORR was all randomized patients that had a measurable disease at baseline. An estimate of ORR and its 95% CI was calculated using the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs between the two arms was determined using the normal approximation to the binomial distribution	(20, 46)
	Chemotherapy	151	12 (8%)								
Stable disease	Atezolizumab	302	122 (40%)	N/A	N/A	N/A	-8%	N/A	N/A		(20, 46)

Results of IPSOS (MO29872)											
				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**		
	Chemotherapy	151	73 (48%)							The analysis population for ORR was all randomized patients that had a measurable disease at baseline. An estimate of ORR and its 95% CI was calculated using the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs between the two arms was determined using the normal approximation to the binomial distribution	
Progressive disease	Atezolizumab	302	67 (22%)	N/A	N/A	N/A	-2%	N/A	N/A	The analysis population for ORR was all randomized patients that had a measurable disease at baseline. An estimate of ORR and its 95% CI was calculated using the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs between the two arms was determined using the normal approximation to the binomial distribution	(20, 46)
	Chemotherapy	151	36 (24%)								
Non-evaluable	Atezolizumab	302	14 (5%)	N/A	N/A	N/A	-3%	N/A	N/A		(20, 46)

Results of IPSOS (MO29872)											
				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		
	Chemotherapy	151	12 (8%)							The analysis population for ORR was all randomized patients that had a measurable disease at baseline. An estimate of ORR and its 95% CI was calculated using the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs between the two arms was determined using the normal approximation to the binomial distribution	
Missing	Atezolizumab	302	48 (16%)	N/A	N/A	N/A	4%	N/A	N/A	The analysis population for ORR was all randomized patients that had a measurable disease at baseline. An estimate of ORR and its 95% CI was calculated using the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs between the two arms was determined using the normal approximation to the binomial distribution	(20, 46)
	Chemotherapy	151	18 (12%)								
Median Duration	Atezolizumab	302	Number of responders: 51 14.0 (8.1-20.3)	N/A	N/A	N/A	6.2	N/A	N/A	DoR is based on a non-randomized subset of patients (specifically, patients who achieve an objective response);	(20, 46)

Results of IPSOS (MO29872)											
				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**		
of response, months										therefore, formal hypothesis testing will not be performed for this endpoint.	
	Chemotherapy	151	Number of responders: 12 7.8 (4.8-9.7)								





Appendix C. Comparative analysis of efficacy

N/A

IPSOS (MO29872) is a head-to-head study which provide a direct comparison of atezolizumab and platinum-based chemotherapy regimens. Results are presented in Appendix B.

Table 45 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Example: median overall survival	NA	NA	NA	NA	NA	NA	NA	NA	NA
Example: 1-year survival	NA	NA	NA	NA	NA	NA	NA	NA	NA
Example: HRQoL	NA	NA	NA	NA	NA	NA	NA	NA	NA
Insert outcome 4	NA	NA	NA	NA	NA	NA	NA	NA	NA

Appendix D. Extrapolation

D.1 Extrapolation of [effect measure 1]

N/A

D.1.1 Data input

N/A

D.1.2 Model

N/A

D.1.3 Proportional hazards

N/A

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

N/A

D.1.5 Evaluation of visual fit

N/A

D.1.6 Evaluation of hazard functions

N/A

D.1.7 Validation and discussion of extrapolated curves

N/A

D.1.8 Adjustment of background mortality

N/A

D.1.9 Adjustment for treatment switching/cross-over

N/A

D.1.10 Waning effect

N/A

D.1.11 Cure-point

N/A

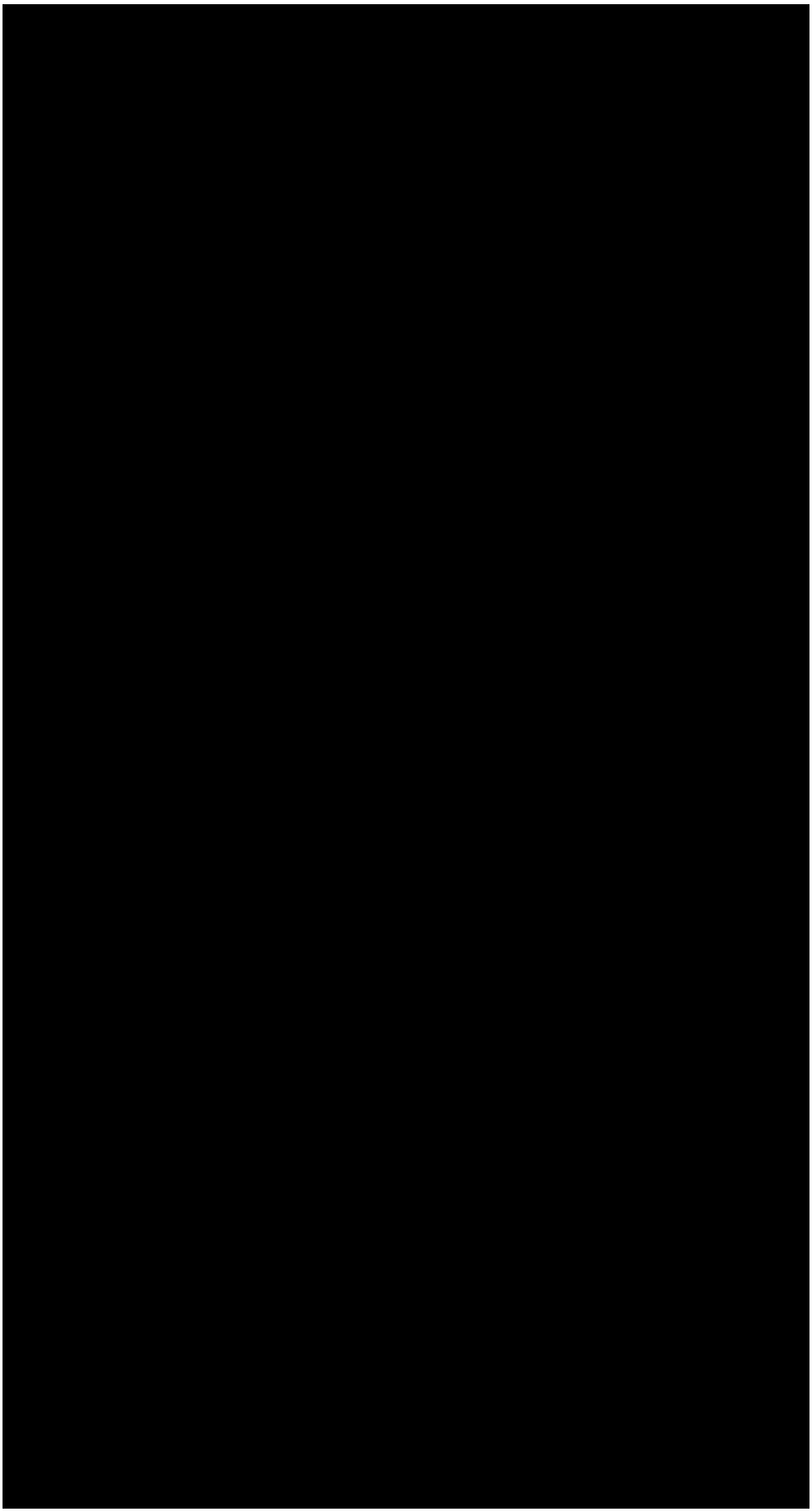
D.2 Extrapolation of [effect measure 2]

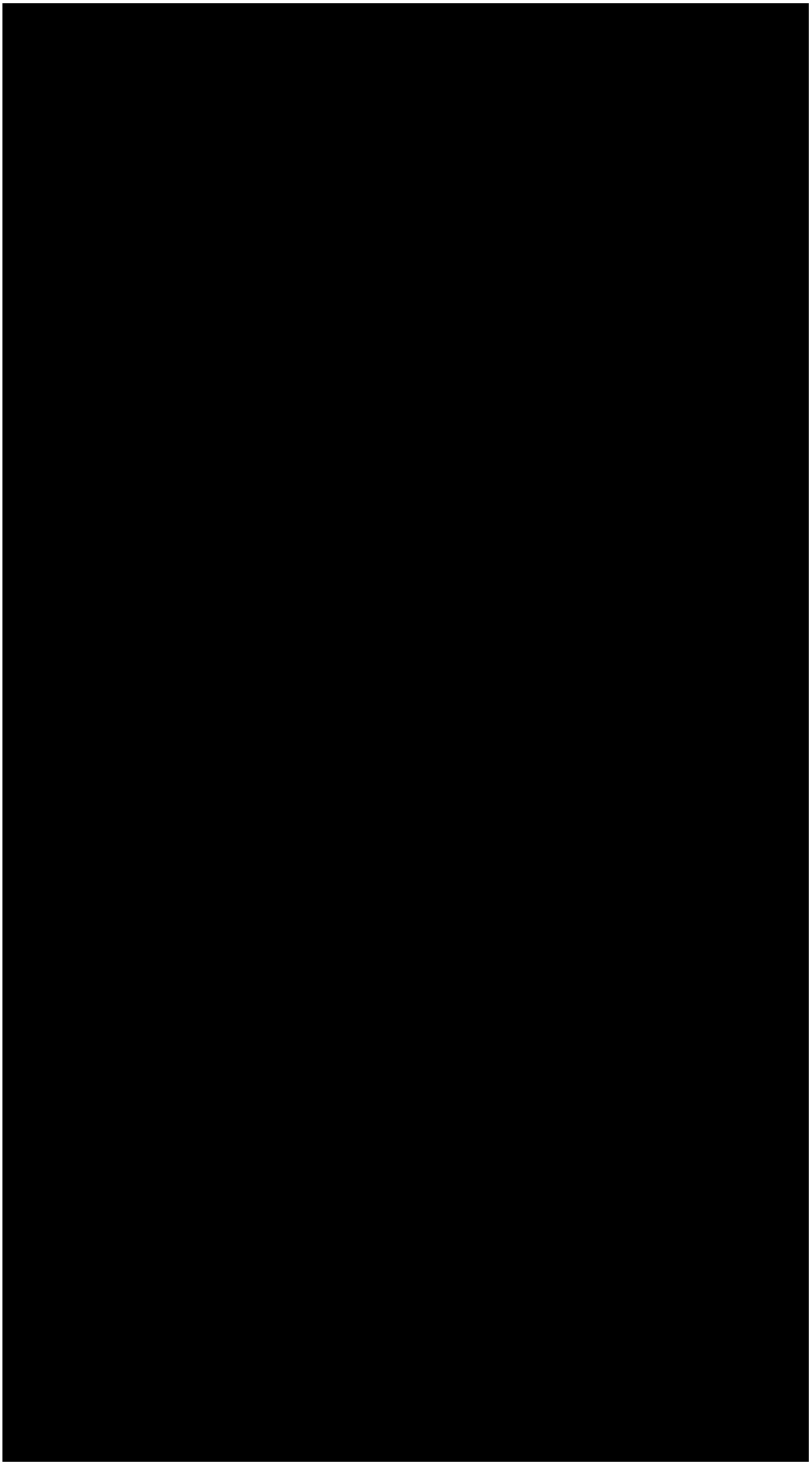
N/A

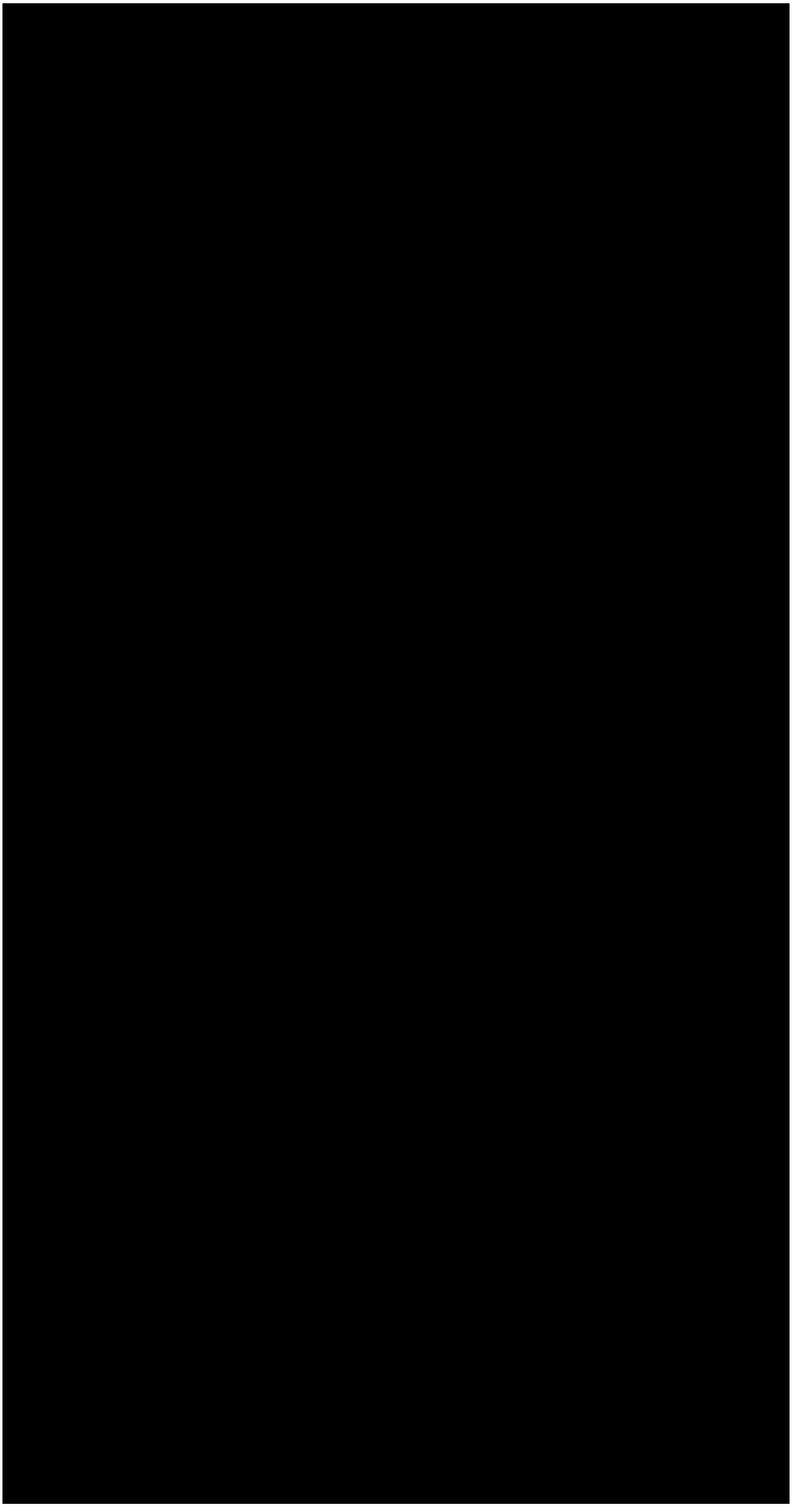
Appendix E. Serious adverse events

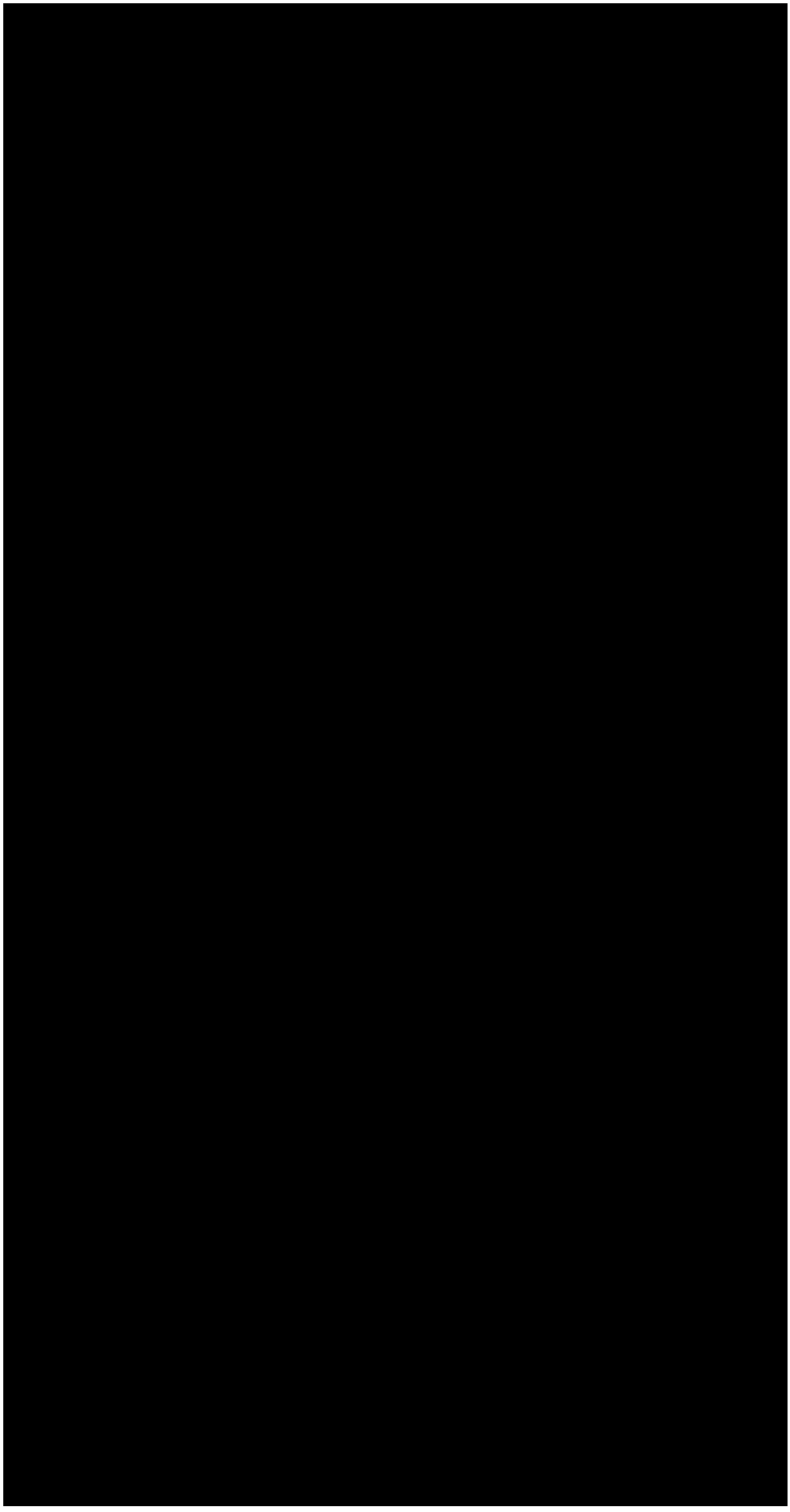
Table 46 List of all Serious Adverse Events by System Organ Class and Preferred Term in the Safety-Evaluable population (23).

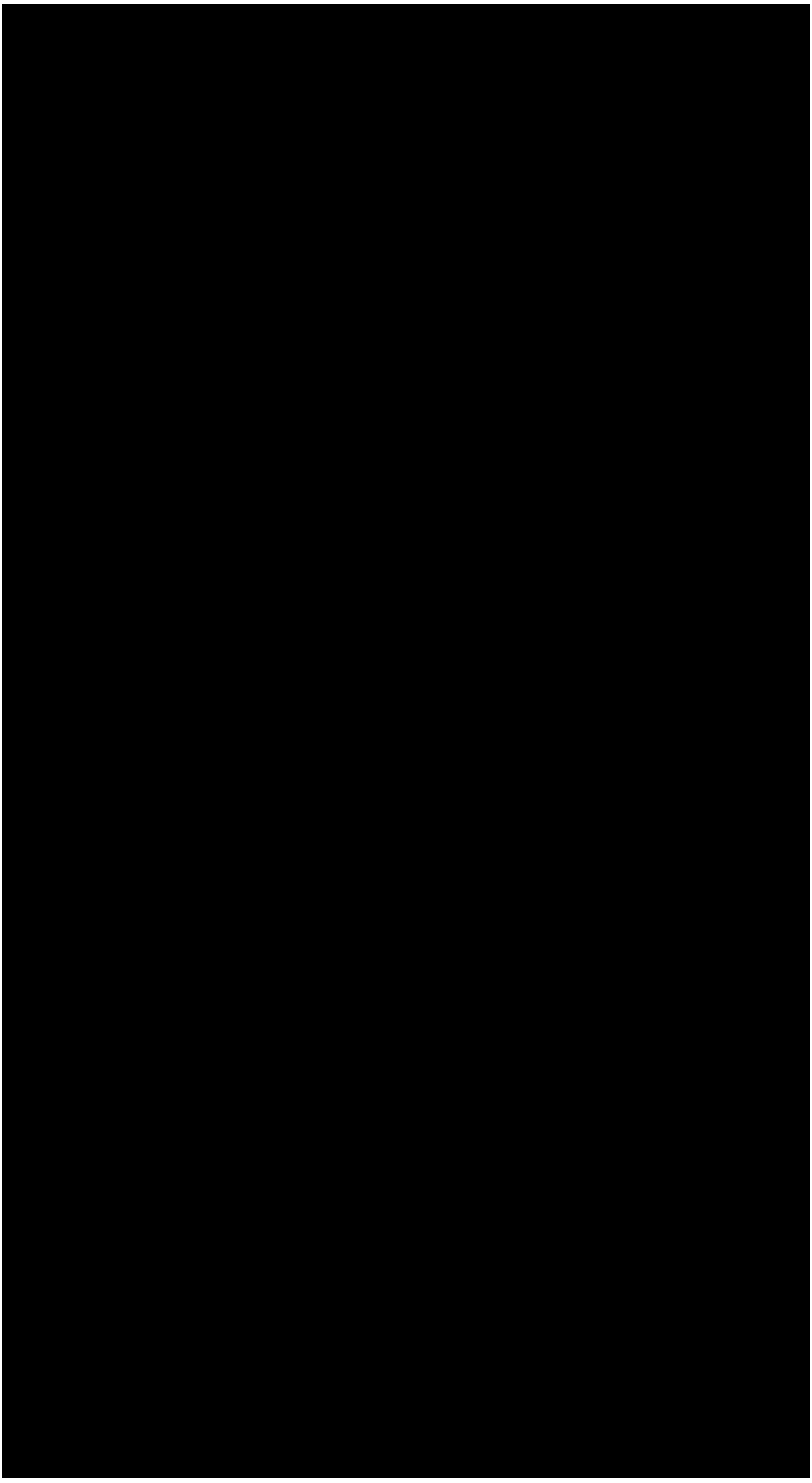
MedDRA System Organ Class MedDRA Preferred Term	Atezolizumab (N=300) n (%)	Chemotherapy (N=147) n(%)
[redacted]		



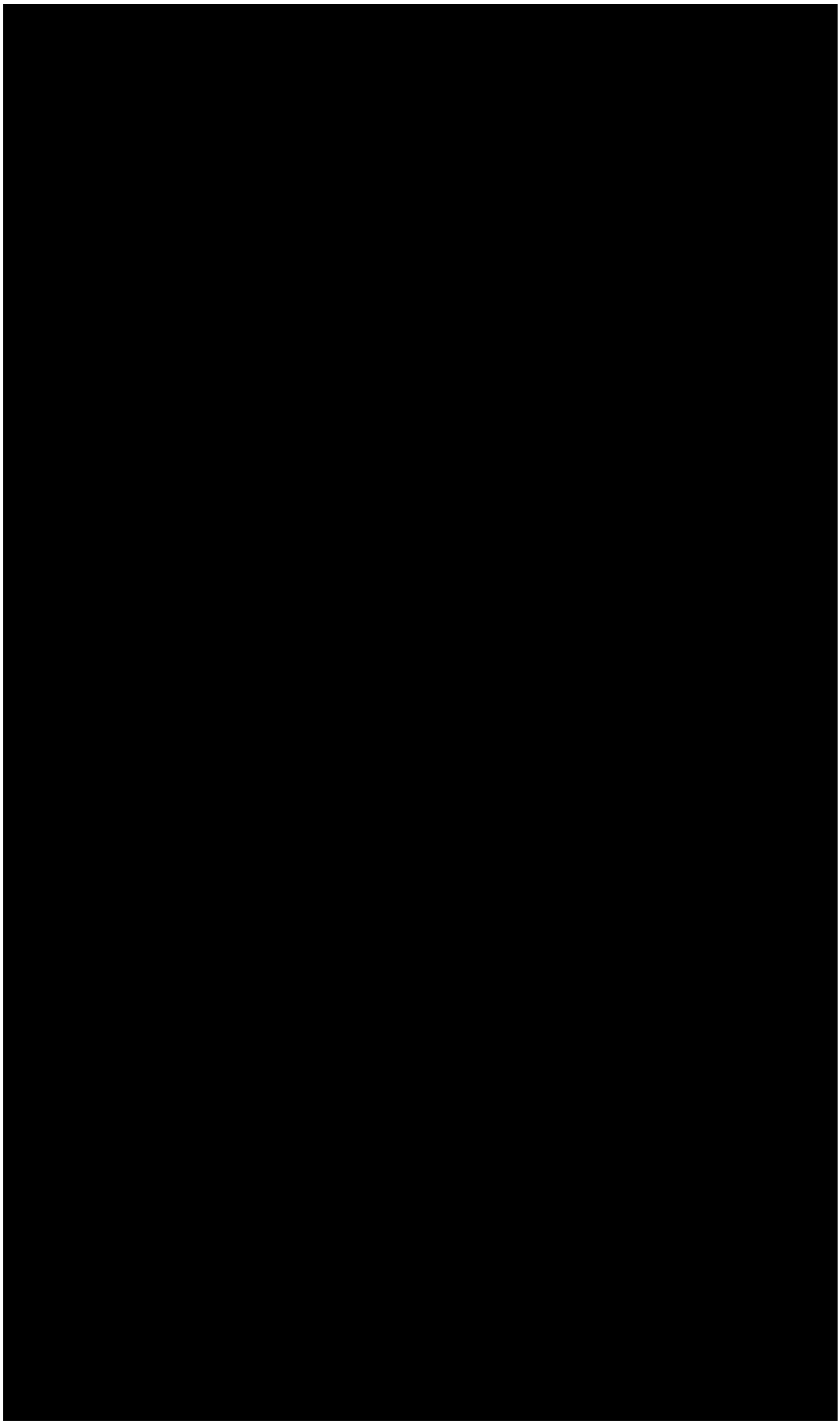








Appendix F. Health-related quality of life



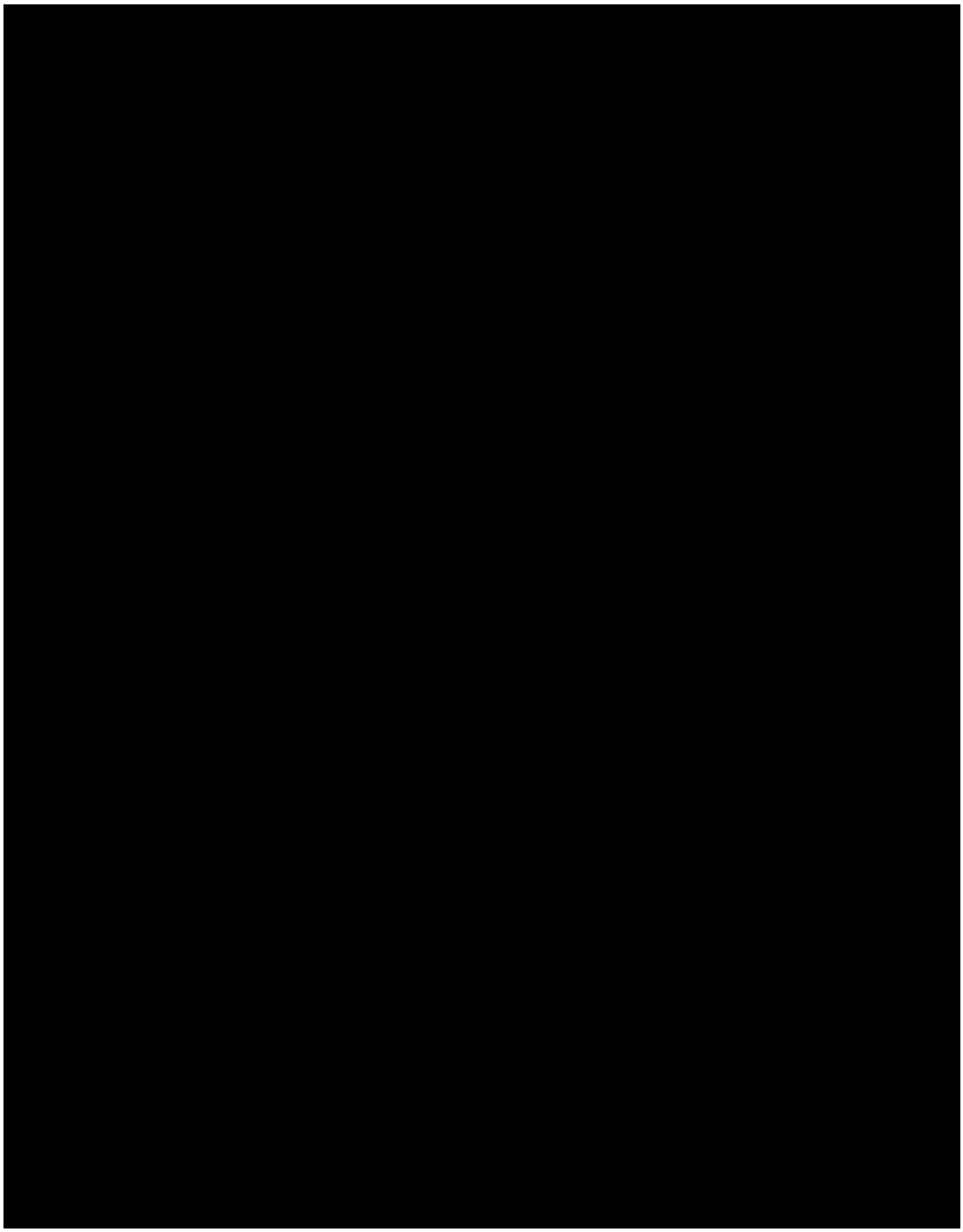
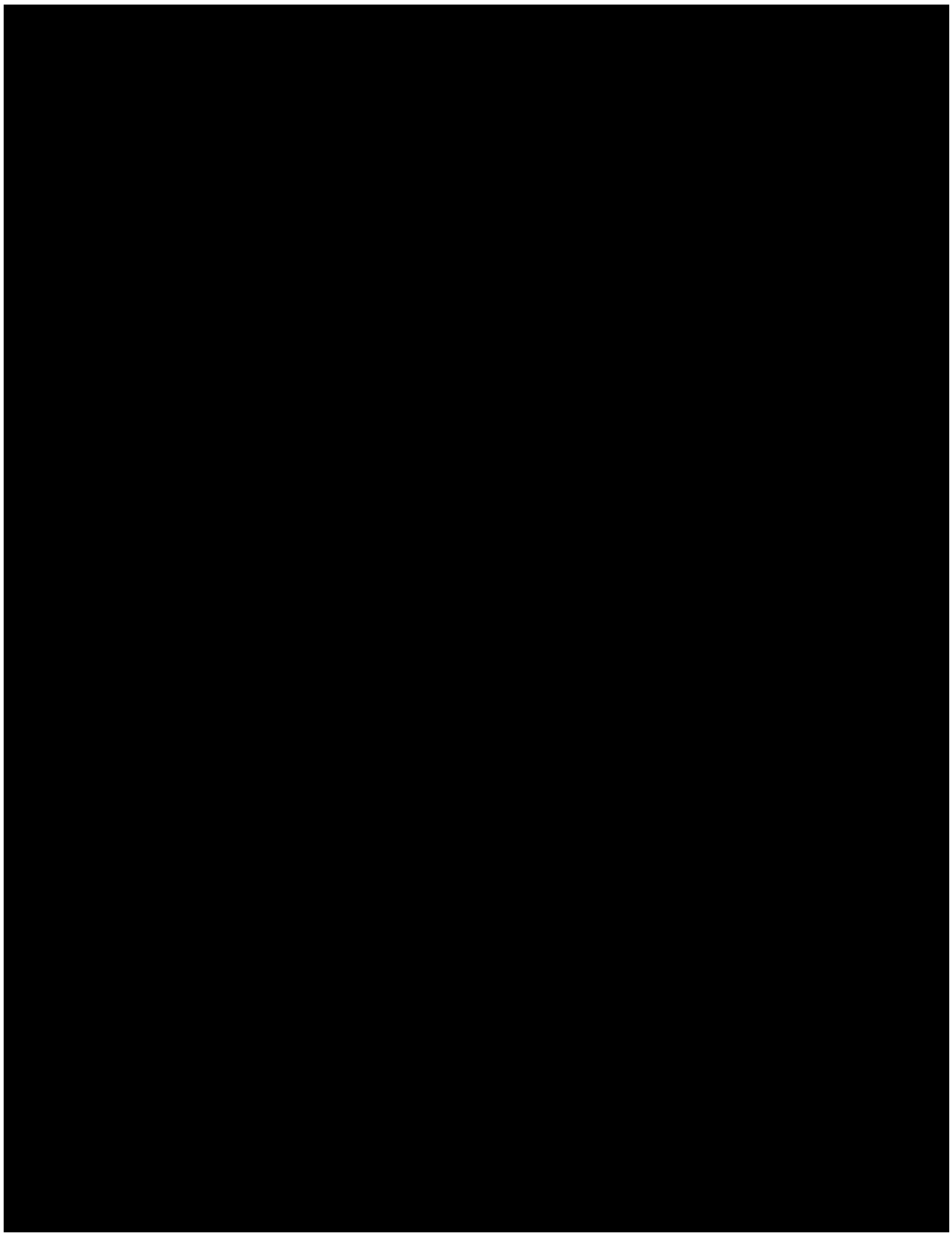
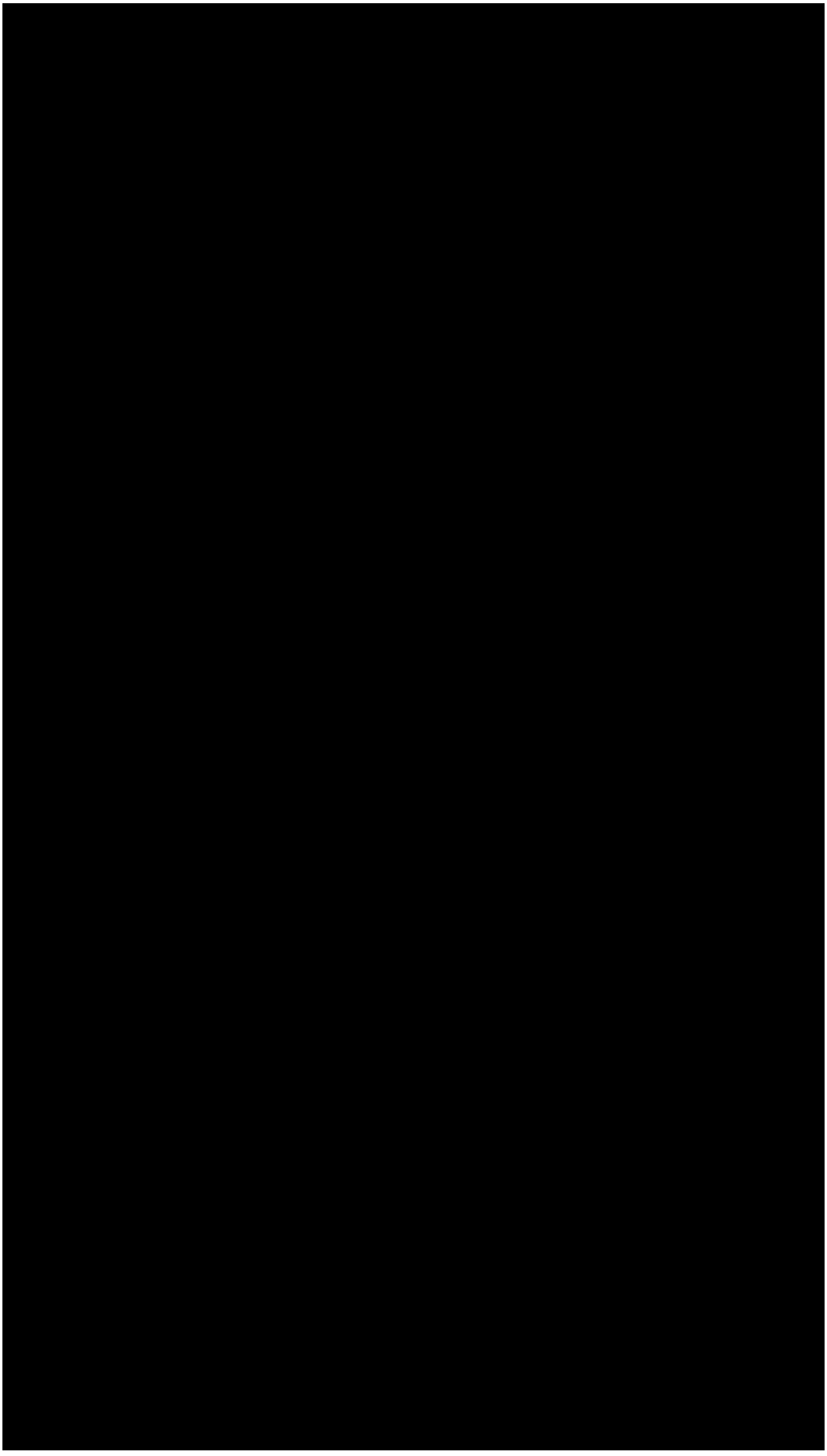
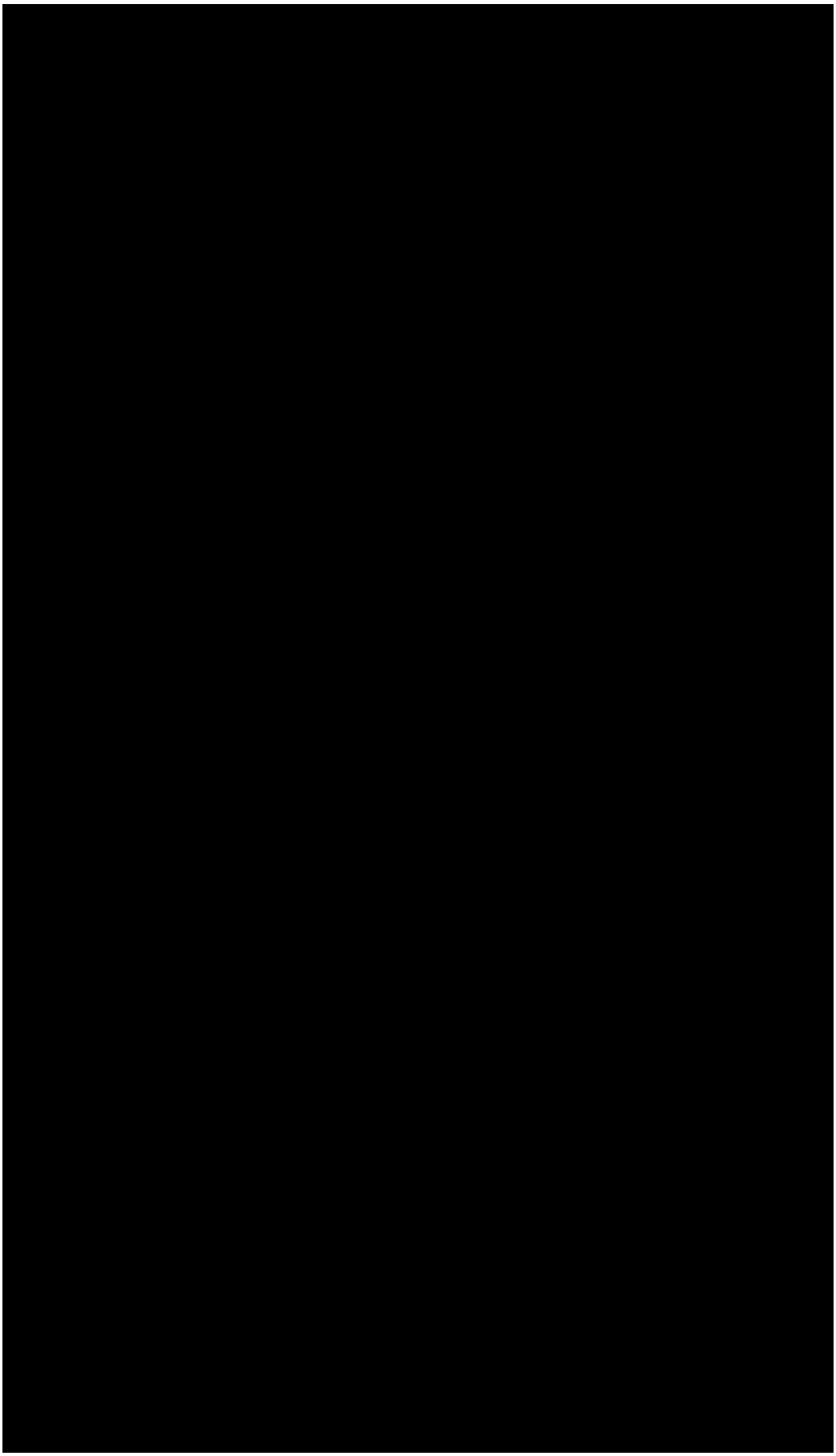


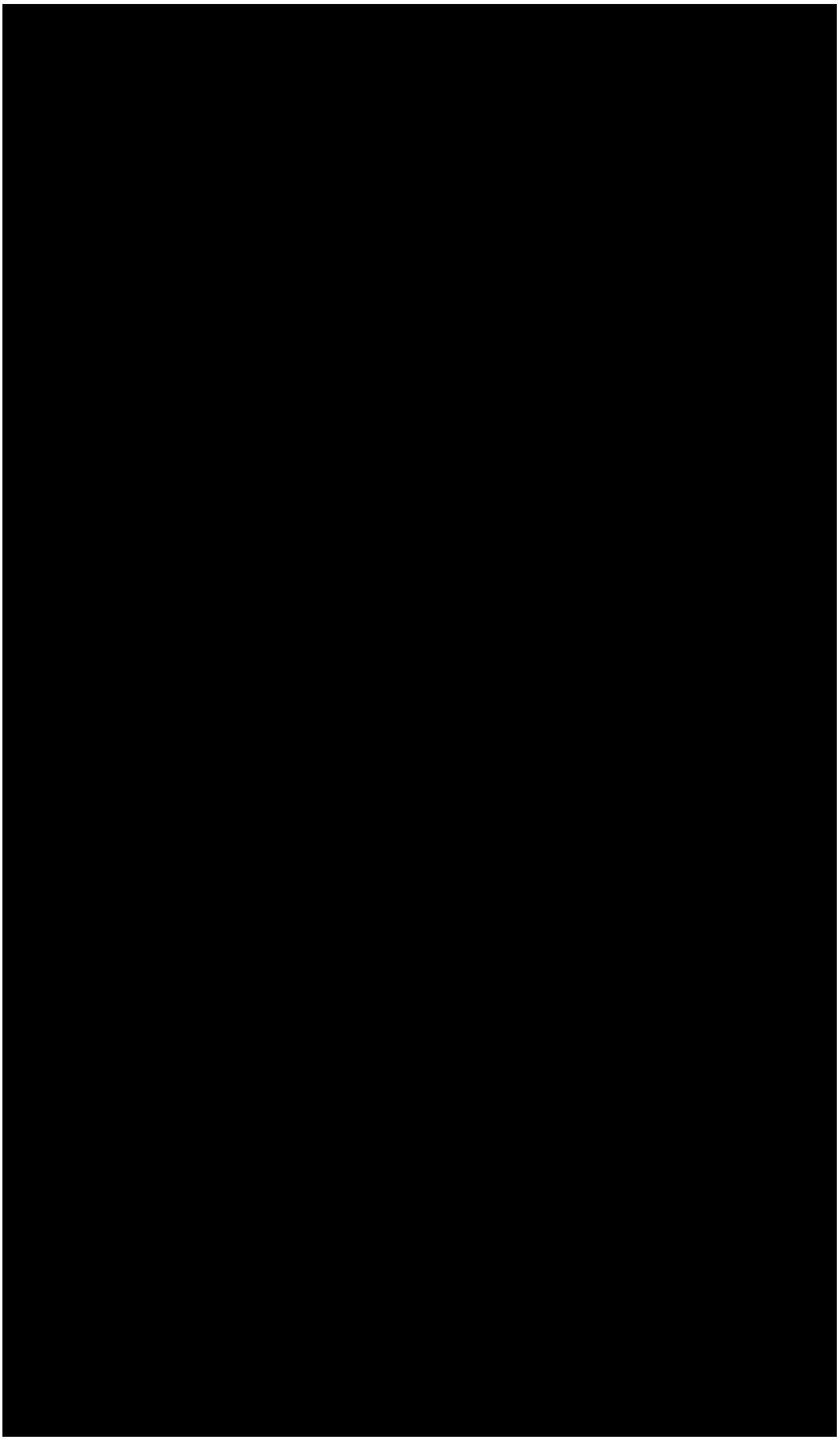
Table 47 EORTC QLQ-LC13 Symptoms in Lung Cancer Scores and Change from Baseline in the ITT population (23).

	Atezolizumab		Chemotherapy		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Dyspnoea					









Appendix G. Probabilistic sensitivity analyses

Table 48. Overview of parameters in the PSA

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

Appendix H. Literature searches for the clinical assessment

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

Table 49 Bibliographic databases included in the literature search

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

Abbreviations:

Table 50 Other sources included in the literature search

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

Abbreviations:

Table 51 Conference material included in the literature search

Conference	Source of ab-stracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A	N/A	N/A	N/A

H.1.1 Search strategies

Table 52 of search strategy table for [name of database]

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

H.1.2 Systematic selection of studies

Table 53 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	N/A	N/A	N/A
Intervention	N/A	N/A	N/A
Comparators	N/A	N/A	N/A

Outcomes	N/A	N/A	N/A
Study design/publication type	N/A	N/A	N/A
Language restrictions	N/A	N/A	N/A

Table 54 Overview of study design for studies included in the analyses

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

H.1.3 Excluded fulltext references

N/A

H.1.4 Quality assessment

N/A

H.1.5 Unpublished data

N/A

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

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

N/A as IPSOS contain HRQoL data

Table 55 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
Specific health economics data-bases[1]	N/A	N/A	N/A

Abbreviations:

Table 56 Other sources included in the literature search

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

Table 57 Conference material included in the literature search

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

I.1.1 Search strategies

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

N/A

Table 58 Search strategy for [name of database]

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

Literature search results included in the model/analysis:

I.1.2 Quality assessment and generalizability of estimates

N/A

I.1.3 Unpublished data

N/A

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

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

N/A

J.1.1 Example: Systematic search for […]

N/A

Table 51 Sources included in the search

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

Abbreviations:

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

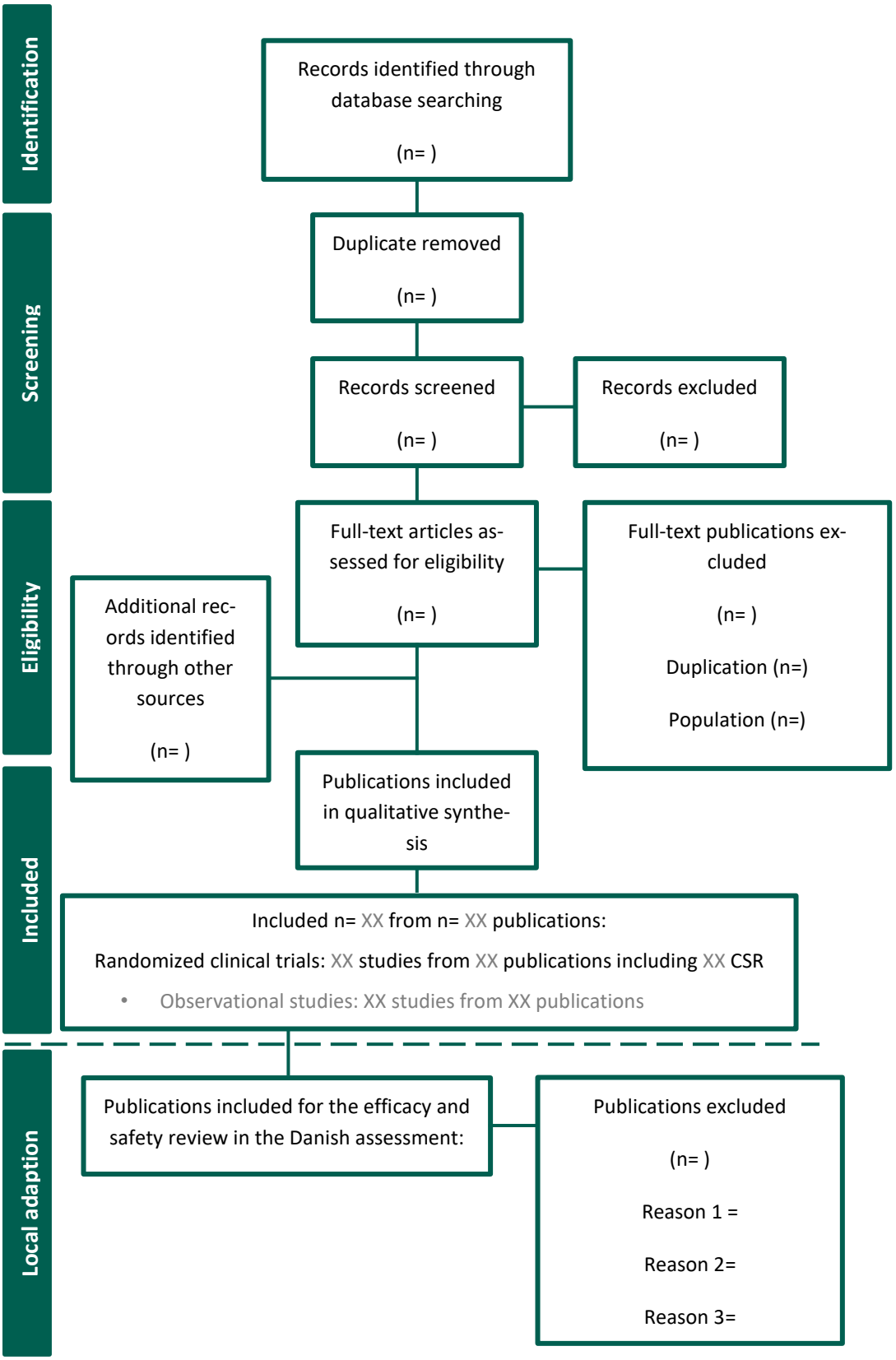
N/A

Table 52 Sources included in the targeted literature search

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

Abbreviations:

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



Appendix K. Other therapeutic indications approved by EMA

This appendix provides information on other indications approved by European Medicines Agency (EMA) for Tecentriq (atezolizumab) (1).

Urothelial carcinoma (UC)
Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic UC:

- after prior platinum-containing chemotherapy, or
- who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%.

Early-stage non-small cell lung cancer (NSCLC)
Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with 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.

Metastatic NSCLC
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 immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC.

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.

Small cell lung cancer (SCLC)
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 (TNBC)
Tecentriq in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumours have PDL1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.

Hepatocellular carcinoma (HCC)
Tecentriq, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy.

Appendix L. Other therapeutic that have been evaluated by the Danish Medicine council

Overview of indications evaluated by DMC on Tecentriq (atezolizumab)

Tabel 1 - Overview of indications evaluated by DMC on Tecentriq (atezolizumab)

Disease area	Usage	Drug
Cancer pulmonis	SCLC	Tecentriq (atezolizumab) in combination with carboplatin and etopside
Cancer pulmonis	Adjuvant treatment of patients with NSCLC	Tecentriq (atezolizumab)
Cancer pulmonis	1 line treatment of NSCLC with PD-L1 > 50%	Tecentriq (atezolizumab)
Cancer pulmonis	NSCLC	Tecentriq (atezolizumab)
Breast cancer	Local progressed or metastatic triple negative breast cancer	Tecentriq (atezolizumab)
Hepatocellular carcinoma	Hepatocellular carcinoma	Tecentriq (atezolizumab in combination with Avastin (bevacizumab)
Cancer in bladder and urinary tract	Urothelial carcinoma	Tecentriq (atezolizumab)

Appendix M. Subsequent treatment in IPSOS study

Table 59 Overview of subsequent treatment in IPSOS. Non-protocol subsequent anti-cancer therapies for patients in the atezolizumab and chemotherapy arms. At each level of summation, patients reporting more than one subsequent therapy are counted only once. Treatments are coded using the WHO Drug Global B3 Format dictionary (46).

	Atezolizumab (n=302)	Chemotherapy (n=151)
[redacted]		

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