Medicinrådet

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

Vers. 2.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. atezolizumab + kemoterapi
2. Ansøgers endelige ansøgning vedr. atezolizumab + kemoterapi

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27.08.2024
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	25.09.2024
Leverandør	Roche
Lægemiddel	Tecentriq (atezolizumab)
Ansøgt indikation	Tecentriq er i kombination med carboplatin og etoposid indiceret til førstelinjebehandling af voksne patienter med småcellet lungekræft i udvidet sygdomsstadie (ES-SCLC)
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende pris på Tecentriq (atezolizumab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Tecentriq	840 mg	1 stk.	20.265,86	[redacted]	[redacted]
Tecentriq	1.200 mg	1 stk.	28.952,64	[redacted]	[redacted]
Tecentriq	1.875 mg	1 stk.	28.577,15	[redacted]	[redacted]

Aftaleforhold

Amgros har en aftale på Tecentriq i perioden 01.01.2024 - 31.12.2025, med mulighed for prisregulering sammen med Opdivo (nivolumab), Keytruda (pembrolizumab), Imfinzi (durvalumab), Libtayo (cemiplimab) og Bavencio (avelumab).

Konkurrencesituationen

[redacted]

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Tecentriq	1.200 mg	1 stk.	1.200 mg IV hver 3. uge	[redacted]	[redacted]
Imfinzi	50 mg/ml	10 ml	1.500 mg IV hver 3. uge i 4 cykler. Herefter 1.500 mg. IV hver 4. uge.	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

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

Konklusion

[redacted]

Application for the assessment of Tecentriq (atezolizumab) for extensive stage small cell lung cancer

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
	Not applicable for application (14 weeks process)
[Other]	[Definition of color-code]

Contact information

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Abbreviations

1L	First-line
CCOD	Clinical cut-off date
ES-SCLC	Extensive stage small cell lung cancer
SCLC	Small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PFS	Progression free survival
1L ES-SCLC	First-line Extensive stage small cell lung cancer
ESMO	European Society for Medical Oncology
RWD	Real World Data
RECIST	Response Evaluation Criteria in Solid Tumours
CP/ET	Carboplatin plus etoposide
ITT	Intention to treat
AE	Adverse Event

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Tecentriq
Generic name	atezolizumab
Therapeutic indication as defined by EMA	First-line extensive stage small cell lung cancer (1L ES-SCLC)
Marketing authorization holder in Denmark	Roche Pharmaceutical A/S
ATC code	L01XC32
Combination therapy and/or co-medication	Carboplatin and etoposide
Date of EC approval	September 6th 2019
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	N/A
Orphan drug designation (include date)	N/A
Other therapeutic indications approved by EMA	Several indications, provided in Appendix I
Other indications that have been evaluated by the DMC (yes/no)	Several indications, provided in Appendix J
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? Atezolizumab for 1L ES-SCLC is already approved for 1L ES-SCLC in the other Nordic countries (Sweden and Norway)
Dispensing group	BEGR

Overview of the medicine	
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, 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) (1).
Dosage regiment and administration	Intravenous (1): Induction and maintenance phases: - 840 mg every 2 weeks or - 1 200 mg every 3 weeks or - 1 680 mg every 4 weeks Tecentriq should be administered first, when given with other treatments on the same day. Induction phase for combination partners (four cycles): Carboplatin, and then etoposide are administered on day 1; etoposide is also administered on days 2 and 3 of each 3-weekly cycle Subcutaneous (1): Induction and maintenance phases: - 1 875 mg every 3 weeks Tecentriq should be administered, first when given with other treatments on the same day. Induction phase for combination partners (four cycles): Carboplatin, and then etoposide is administered on day 1; etoposide is also administered on days 2 and 3 of each 3-weekly cycle.
Choice of comparator	Carboplatin and etoposide
Prognosis with current treatment (comparator)	Small cell lung cancer (SCLC) is a very aggressive disease. Most patients are diagnosed late with extensive disease(2). RWD on Danish patients was published in 2020. Here the median survival for extensive disease was 6.2 and the 5-year survival rate was 2% (3).

Summary	
Type of evidence for the clinical evaluation	Head-to-head study
Most important efficacy endpoints (Difference/gain compared to comparator)	Overall survival (OS): Treatment arm had an OS of 12.3 months, whereas the comparator had 10.3 months, resulting in a gain of 2 months with treatment. HR 0.76 (0.60-0.95) Progression free survival (PFS): Treatment arm had a PFS of 5.2 months, whereas the comparator had 4.3 months, resulting in a gain of 0.9 months with treatment. Hazard Ratio (HR) 0.77 (0.63-0.95)
Most important serious adverse events for the intervention and comparator	Most frequent grade 3-4 serious treatment related adverse events in the atezolizumab and carboplatin plus etoposide (CP/ET) arm was neutropenia 6 (3.0 %) patients, thrombocytopenia 5 (2.5 %) patients, febrile neutropenia 4 (2.0 %) patients. In the CP/ET arm it was febrile neutropenia 9 (4.6%) patients, neutropenia 8 (4.1 %) patients and thrombocytopenia in 4 (2.0) patients. In arms of IMpower133 3 (1.5%) deaths occurred in the atezolizumab combined with CP/ET it was neutropenia, pneumonia and unspecified. In the placebo + CP/ET arm deaths was related to pneumonia, cardiopulmonary failure and septic chock.
Impact on health-related quality of life	In general, no notable differences in treatment-related symptoms (e.g. diarrhea, sore mouth) were observed between arms at induction visits, at the end of induction. Positive trends of improvement in some symptoms (e.g. nausea/vomiting, fatigue, insomnia, appetite loss) were reported by patients in both arms. Time to meaningful worsening of treatment-related symptoms (e.g. peripheral neuropathy, alopecia) was also similar between arms. Notably, there were few deterioration events in each arm. Considering the broader impact of symptoms on patients' global health status, while HRQoL improved in both arms, clinically meaningful improvements persisted in the atezolizumab plus CP/ET arm through week 54, suggesting that the survival benefit achieved with the addition of atezolizumab to CP/ET was associated with minimal impact on treatment-related symptoms. Taken together, the notable HRQoL improvements reported by patients in the atezolizumab arm suggest that the addition of atezolizumab to CP/ET did not increase toxicity or symptom burden (20)
Type of economic analysis that is submitted	N/A

Summary	
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	[Describe the model assumptions with the largest overall impact on the incremental costs and QALY gain]
Number of eligible patients in Denmark	Incidence: Approximately 12,5% (4) Prevalence: Approximately 600 (4)
Budget impact (in year 5)	N/A

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

3.1 The medical condition

Small cell lung cancer (SCLC) is an aggressive subtype of lung cancer that is associated with limited treatment options and poor prognosis (2). The cause of SCLC are strongly linked to smoking, and often inactivation of different tumor suppressor genes like p53 and RB, which are also found in a majority of SCLC patients (2). Due to the aggressiveness of the disease and the limited treatment options, patients suffering from SCLC in general have a poor prognosis (2, 3).

Due to the nature and location of the disease, patients are often symptomatic at diagnosis and the duration of the symptoms are often short due to the rapid development (2). Symptoms of SCLC include coughing, wheezing, dyspnoea,

haemoptysis, oedema and flushing in the upper body due to superior vena cava compression, oesophageal compression with dysphagia, and recurrent laryngeal nerve compression with left vocal cord paralysis (2). SCLC metastasis are often seen in brain, liver, adrenal glands as well as bone and bone marrow (2).

3.2 Patient population

In Denmark, approximately 4.500 patients are diagnosed with lung cancer every year. Lung cancer is therefore one of the most common cancer diseases (4). There are two major types of lung cancer: SCLC and non-small cell lung cancer (NSCLC). Approximately 15% of the patients in Denmark are diagnosed with SCLC (Table 1) (4). SCLC is an aggressive disease, that is characterized by rapid progression and a high likelihood of early metastatic disease (2, 3, 5). Patients with extensive stage SCLC (ES-SCLC) have a poor overall survival if not treated (5). In a Danish registry study by Green et al from 2020 the median survival for ES-SCLC was 6.2 months and the 5 year survival rate was only 2% (3).

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark*	12,9% (4)	13,0% (4)	12,1% (4)	12,0 % (4)	N/A (4)
Prevalence in Denmark	652 (4)	614 (4)	622 (4)	608 (4)	N/A (4)
Global prevalence	N/A	N/A	N/A	N/A	N/A

* Of all lung cancer patients in Denmark

The patient population relevant for this application covers the Tecentriq indication on SCLC: *Tecentriq, in combination with carboplatin and etoposide, is indicated for the first line (1L) treatment of adult patients with ES-SCLC (1).* For the estimated number of patients eligible for treatment, see Table 2. ES-SCLC constitute around two thirds of all newly diagnosed SCLC patients.

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	155 (6)	155 (6)	155 (6)	155 (6)	155 (6)

3.3 Current treatment options

Currently, the Danish clinical practice is to use carboplatin and etoposide for 1L treatment of patients with ES-SCLC (5, 6).

In the latest reassessment of atezolizumab for 1L ES-SCLC, H2 2020, The Danish Medicines Council concluded that atezolizumab in combination with carboplatin and etoposide collectively had a better efficacy as compared to carboplatin and etoposide alone (6). More than 34 European countries including Sweden, Norway and other comparable countries have recommended and reimbursed the use of atezolizumab in combination with carboplatin and etoposide in 1L ES-SCLC patients.

Besides atezolizumab, both durvalumab and serplulimab has shown positive data in 1L ES-SCLC patients in the CASPIAN, LUMINANCE and ASTRUM-005 studies (7-9).

Furthermore, ESMO Clinical Guidelines recommend the use of atezolizumab in combination with carboplatin and etoposide for 1L treatment of ES-SCLC patients with performance status 0-1 (10).

3.4 The intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	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) (1).
Method of administration	Intravenous or subcutaneous (1).
Dosing	Intravenous (1): Induction and maintenance phases: - 840 mg every 2 weeks or - 1 200 mg every 3 weeks or - 1 680 mg every 4 weeks Tecentriq should be administered first when given with other treatments on the same day.

Overview of intervention	
	Induction phase for combination partners (four cycles): Carboplatin, and then etoposide are administered on day 1; etoposide is also administered on days 2 and 3 of each 3-weekly cycle Subcutaneous (1): Induction and maintenance phases: - 1 875 mg every 3 weeks Tecentriq should be administered first when given with other treatments on the same day. Induction phase for combination partners (four cycles): Carboplatin, and then etoposide are administered on day 1; etoposide is also administered on days 2 and 3 of each 3-weekly cycle.
Should the medicine be administered with other medicines?	In ES-SCLC Tecentriq should be given in combination with carboplatin and etoposide (1).
Treatment duration / criteria for end of treatment	Until disease progression or unmanageable toxicity. Treatment beyond disease progression may be considered at the discretion of the physician (1).
Necessary monitoring, both during administration and during the treatment period	Standard monitoring with CT scan etc.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	N/A
Package size(s)	1 vial - 840 mg/14 mL for infusion 1 vial - 1200 mg/20 mL for infusion 1 vial - 1875 mg/15 mL for injection

3.4.1 The intervention in relation to Danish clinical practice

Atezolizumab will be added to the current standard of care, consisting of carboplatin and etoposide. Therefore, implementation of atezolizumab will not alter the treatment algorithm.

3.5 Choice of comparator(s)

Currently the standard of care for 1L ES-SCLC is 4-6 cycles of carboplatin and etoposide (5). The recommendation is based on several meta-analysis and literature reviews (11-

13). There are limited treatment options beyond 1L treatment. Depending on whether the patient has sensitive or refractory disease, reintroduction to carboplatin and etoposide or second line chemotherapy could be possible treatment options (5).

Overview of comparator	
Generic name	Carboplatin and etoposide
ATC code	L01XA02 (carboplatin) L01CB01 (etoposide)
Mechanism of action	Cytostatic (carboplatin) Cytostatic, topoisomerase inhibitor (etoposide)
Method of administration	Intravenous Infusion
Dosing	Induction phase for combination partners (four cycles): Carboplatin, and then etoposide are administered on day 1; etoposide is also administered on days 2 and 3 of each 3-weekly cycle.(1)
Should the medicine be administered with other medicines?	Carboplatin and etoposide
Treatment duration/ criteria for end of treatment	4-6 cycles (5)
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	See section 3.4

3.6 Relevant efficacy outcomes

3.6.1 Definition of efficacy outcomes included in the application

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS) IMpower133 (14) IMbrella A(15)		OS, defined as the time from randomization to death from any cause (17)	IMpower133: Kaplan–Meier methodology was used to estimate the probability of OS, as well as to calculate the median time from randomization to death (for

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
SKYSCRAPER-02 (16)			OS) for each group, and the Brookmeyer and Crowley method was used to construct the 95% confidence interval (95% CI) for the medians. The hazard ratios (HR) and 95% CI for OS were estimated with the use of a stratified Cox regression model, with the same stratification factors that were used in the stratified log-rank test For SKYSCRAPER-02: The HR for OS was estimated using a stratified Cox proportional hazards model. Kaplan-Meier methodology was used to estimate median OS, and the Brookmeyer-Crowley method was used to construct 95% CIs
Progression survival (PFS) (investigator assessed, per RECIST 1.1) IMpower133 (14) SKYSCRAPER-02 (16)		PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first (17, 18)	IMpower133: Kaplan–Meier methodology was used to estimate the probability of PFS, as well as to calculate the median time from randomization to disease progression or death for each group, and the Brookmeyer and Crowley method was used to construct the 95% CI for the medians. The HR and 95% CI for PFS were estimated with the use of a stratified Cox regression model, with the same stratification factors that were used in the stratified log-rank test For SKYSCRAPER-02: the HR for PFS was estimated using a stratified Cox proportional hazards model. Kaplan-Meier methodology was used to estimate median PFS, and the Brookmeyer-Crowley method was used to construct 95% CIs
Objective response rate		Objective response, defined as PR or CR as determined by	

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
(ORR) (investigator assessed, per RECIST 1.1) IMpower133(14) SKYSCRAPER-02 (16)		the investigator according to RECIST v1.1(17, 18)	

* Time point for data collection used in analysis (follow up time for time-to-event measures)
Abbreviations: CR – Complete Response; PFS – Progression Free Survial; PR – Partial Response; OS – Overall Survival.

Validity of outcomes

The two co-primary endpoints OS and PFS in IMpower133 are well-defined and golden standard endpoints within oncologic research (5). The secondary endpoints in IMpower133, investigator-assessed overall response rate (ORR) per RECIST 1.1 are also well defined and golden standard endpoints within oncologic research (5).

4. Health economic analysis

Not applicable in the 14-weeks process

5. Overview of literature

5.1 Literature used for the clinical assessment

This application is based on a randomized head-to-head clinical trial against the standard of care and two studies as supporting evidence. Roche have applied for re-submission of atezolizumab with carboplatin and etoposide for ES-SCLC and have described the newest data on this intervention, Table 4.

Table 4 Relevant literature included in the assessment of efficacy and safety

Reference	Trial name	NCT identifier	Dates of study	Used in comparison of*
Horn L et al; First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer; N Engl J Med 2018;379:2220-2229 (19). Liu S et al; Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133); J Clin Oncol 39:619-630, Jan 2021 (14).	IMpower133	NCT02763579	Start: 07/06/2016 Primary completion date: 24/04/2018 Study completion date: 07/07/2022	Atezolizumab combined with carboplatin and etoposide vs. carboplatin and etoposide for 1L ES-SCLC
Liu S et al; FIVE-YEAR SURVIVAL IN PATIENTS WITH ES-SCLC TREATED WITH ATEZOLIZUMAB IN IMPOWER133: IMBRELLA A EXTENSION STUDY RESULTS; WCLC congress, Sep 2023 (15).	IMbrella A (IMpower133 extension study)	NCT03148418	Start: 20/09/2017 Completion: 06/03/2030	Atezolizumab combined with carboplatin and etoposide in 1L ES-SCLC
Rudin et al, SKYSCRAPER-02: Tiragolumab in Combination With	SKYSCRAPER-02	NCT04256421	Start: 04/02/2020	Tiragolumab in Combination With Atezolizumab Plus Chemotherapy vs.

Reference	Trial name	NCT identifier	Dates of study	Used in comparison of*
Atezolizumab Plus Chemotherapy in Untreated Extensive-Stage Small-Cell Lung Cancer, J Clin Oncol, Jan 2024(16).			Primary completion date: 06/07/2022 Study completion date: 15/04/2026	Atezolizumab plus chemotherapy in 1L ES-SCLC

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

No literature search for performed for this application, for the HRQoL analysis the PRO data from the IMpower133 study was used.

Table 5 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Mansfield et al Safety and patient-reported outcomes of atezolizumab, carboplatin, and etoposide in extensive-stage small-cell lung cancer (IMpower133): a randomized phase I/III trial Annals of Oncology, January 2020 (20)	First line ES-SCLC in real world setting	Section 10

5.3 Literature used for inputs for the health economic model

As no health economic analysis was performed, no literature search was conducted.

6. Efficacy

6.1 Efficacy of Tecentriq (atezolizumab) in combination with carboplatin and etoposide compared to carboplatin and etoposide for patients in 1L Extensive Stage Small Cell Lung Cancer

6.1.1 Relevant studies

Table 6 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
IMpower133, NCT02763579 **Horn et al (19)** **Liu et al (14)**	Randomized phase I/III, double-blind, placebo-control in combination with CP/ET 1:1	Four 21-days cycles followed by a maintenance phase until disease progression or unacceptable toxicity. Median follow up was 22.9 months	Eligible patients had histologically or cytologically confirmed chemotherapy-naive ES-SCLC. Patients with treated asymptomatic brain metastases were eligible, and those with active or untreated CNS metastases were excluded from the study. Patients were stratified by sex, Eastern Cooperative Oncology Group performance	Four 21-day cycles of CP/ET (CP: area under the curve of 5 mg/mL/min, intravenous [IV] on day 1 of each cycle; ET: 100 mg/m2 of body surface area, IV on days 1-3 of each cycle) plus IV atezolizumab 1,200 mg (atezolizumab plus CP/ET) on day 1 of each cycle (induction phase), followed by the same dose of IV atezolizumab during a	Four 21-day cycles of CP/ET (CP: area under the curve of 5 mg/mL/min, intravenous [IV] on day 1 of each cycle; ET: 100 mg/m2 of body surface area, IV on days 1-3 of each cycle) plus placebo (placebo plus CP/ET) on day 1 of each cycle (induction phase), followed by the same dose of placebo during a maintenance phase until unacceptable	The two primary endpoints were OS (median follow up: 13.9 months) and investigator assessed PFS per RECIST 1.1 in ITT population. Key secondary endpoints were investigator-assessed ORR per RECIST 1.1; DOR; and safety. Median follow up was 22.9 months Exploratory endpoints included assessment of efficacy based on PD-L1 expression levels and bTMB as previously described (19).

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
			status (0 v 1), and presence of brain metastases (yes / no) at enrollment.	maintenance phase until unacceptable toxicity or disease progression. Treatment beyond disease progression was allowed if patients experienced clinical benefit	toxicity or disease progression.	
IMbrella A, NCT03148418 Liu et al (15)	Open-label, non-randomized, multicenter extension and long-term observational study on IMpower133	Maintenance phase of Tecentriq until disease progression or unacceptable toxicity.	Patients in the IMpower133 control arm were not eligible for enrollment in IMbrella A. Patients were eligible if they continued to receive	Tecentriq maintenance phase	NA	Long term overall survival (OS). Follow up was 5 year after IMpower133

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
			Tecentriq at study closure of IMpower133 or were in survival follow-up. Rollover from IMpower133 to IMbrella A for patients treated with Tecentriq in IMpower133 occoured between Dec 2019 and July 2020.			
Skyscraper-02, NCT04256421 Rudin et al (16)	Randomized, placebo-controlled phase III	Assigned randomly 1:1 to receive four 21-day cycles of intravenous (IV) tiragolumab (600 mg once	Eligible patients were age 18 years and older with treatment-naïve, histologically or cytologically confirmed ES-SCLC (per		NA – Active arm with tiragolumab not relevant in this application	OS, PFS and ORR. Two CCODs February 6, 2022 & September 6, 2022.Median follow up time were 14.3 and 21.1 months, respectively.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
		on day 1 of each cycle)	modified Veterans Administration Lung Study Group staging system), measurable disease according to RECIST 1.1, and ECOG PS 0 or 1. Patients with treated or untreated brain metastases were permitted, provided the metastases were asymptomatic and measurable disease was present outside the CNS.			

CCOD – clinical cut-off date; CNS – Central nervous system; ES-SCLC - extended stage small cell lung cancer; OS - overall survival; PFS - progression free survival; IV – intravenous; IIT - intention to treat; ORR - overall response rate; DOR - duration of response; CP - carboplatin ET – etoposide; bTMB - blood tumour mitational burden; PD-L1 - programmed death ligand-1; ECOG – Eastern Cooperative Oncology Group; PS – performance status

6.1.2 Comparability of studies

All three studies (IMpower133, IMbrella A and SKYSCRAPER-02) reports OS, PFS and ORR. IMpower133 (a head-to-head study comparing atezolizumab in combination with carboplatin and etoposide against carboplatin and etoposide) is the primary analysis. IMbrella A and SKYSCRAPER-02 are supportive evidence of IMpower133 – baseline characteristics of SKYSCRAPER-02 is comparable with IMpower133 (14-16).

6.1.2.1 Comparability of patients across studies

Table 7 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	IMpower133 (14)		IMbrella A (15)	SKYSCRAPER-02 (16)
	Atezolizumab + CP/ET, n=201	Placebo + CP/ET, n= 202	Atezolizumab+ CP/ET, n=18	Atezolizumab+ CP/ET, n=247
Age	64 (28-90)	64 (26-87)	60.5 (46-80)	65 (33-83)
Gender male, n (%)	129 (64.2)	132 (65.3)	11 (61.1)	164 (66.4)
Performance status 0/1, n (%)	73 (36.3)/ 128 (63.7)	67 (33.2)/ 135 (66.8)	12 (66.7)/ 6 (33.3)	82 (33.2)/ 165 (66.8)
Brain metastases at inclusion, n (%)	17 (8.5)	18 (8.9)	2 (11.1)	46 (18.6)
Smokers, n (%)				
Never **Previous** **Current**	8 (4) 25 (12.4) 33 (16.4)	12 (5.9) 28 (13.9) 25 (12.4)	1 (5.6)	10 (4) 161 (65.2) 76 (30.8)
Prior cancer treatment(%)			NA	NA
Chemotherapy **Radiation** **Surgery**	8 (4) 25 (12.4) 33 (16.4)	12 (5.9) 28 (13.9) 25 (12.4)		

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

In the table below data on a relevant Danish population and the population of IMpower133 is compared.

Table 8 Characteristics in the relevant Danish population and in the health economic model

	Danish population (3)	IMpower133 (14)	Value used in health economic model (reference if relevant)
Mean age, years	68.5	NR	
Gender, Male %	50.8	64.2	
LS-SCLC, %	25.7	0	
ES-SCLC, %	68.2	100	
≥1 co-morbidity, %	37.1	NR	
ECOG PS, %			
0		36.3	
1		63.7	

NR - not reported; LS-SCLC - Limited-stage small cell lung carcinoma; ES-SCLC - Extended-stage small cell lung carcinoma; ECOG - Eastern Cooperative Oncology Group; PS - performance status

In general, the Danish population that candidates to treatment with atezolizumab in combination with carboplatin plus etoposide (CP/ET) are comparable to the study population in IMpower133.

6.1.4 Efficacy – results per IMpower133

IMpower133 is a randomized, double-blind, phase I/III study, that demonstrated that adding atezolizumab to carboplatin plus etoposide (CP/ET) for 1L treatment of ES-SCLC resulted in significant improvement in OS and PFS versus placebo plus CP/ET. The two primary endpoints, investigator-assessed PFS and OS, were statistically significant at the interim analysis. Updated OS and PFS were conducted in the updated analysis by Liu et al (14). Clinical cut-off date (CCOD) for OS and PFS were January 24 2019 and April 4 2018, respectively.

The median OS was 12.3 months (95% CI, 10.8 to 15.8) in the atezolizumab plus CP/ET arm and 10.3 months (95% CI, 9.3 to 11.3) in the placebo plus CP/ET arm (HR, 0.76; 95% CI, 0.60 to 0.95). OS at 12 months demonstrated a survival increase of 12.9% in the atezolizumab plus CP/ET arm (51.9%) compared with the placebo plus CP/ET arm (39.0%). Similarly, at 18 months, 13.0% more patients were alive in the atezolizumab plus CP/ET arm (34.0%) than with placebo plus CP/ET (21.0%). Consistent with results observed at the primary analysis of IMpower133, the addition of atezolizumab was associated with consistent OS benefit across the majority of subgroups. At the updated analysis, confirmed ORRs in the intention to treat (ITT) population were 60.2% in the atezolizumab plus CP/ET arm (95% CI, 53.1 to 67.0) versus 64.4% (95% CI, 57.3 to 71.0; descriptive P 5 .3839) in the placebo plus CP/ET arm. The median DOR was 4.2 months (95% CI, 4.1 to 4.5) in the atezolizumab plus CP/ET arm versus 3.9 months (95% CI, 3.1 to 4.2) in the placebo plus CP/ET arm (HR, 0.67; 95% CI, 0.51 to 0.88; descriptive P 5 .0037).

At the updated analysis, 181 patients (90.0%) in the atezolizumab plus CP/ET arm and 194 patients (96.0%) in the placebo plus CP/ET arm had RECIST-defined disease progression. Median PFS in the ITT population at the updated analysis was 5.2 months (95% CI, 4.4 to 5.6) in the atezolizumab plus CP/ET arm and 4.3 months (95% CI, 4.2 to 4.5) in the placebo plus CP/ET arm (HR, 0.77; 95% CI, 0.63 to 0.95). Disease progression occurred with the following patterns in the atezolizumab plus CP/ET and placebo plus CP/ET arms, respectively: 57.7% and 64.9% at existing lesions, 42.8% and 49.0% at new lesions, and 20.9% and 28.2% at both new and existing lesions (14).

6.1.5 Efficacy – results per IMbrella A

IMbrella A is an open-label, non-randomised, multicenter and long-term observational study and an extension study of IMpower133 (15). At the time of IMpower133 study closure, patients treated with atezolizumab in combination with carboplatin and etoposide were eligible to enroll in the Phase IV, single-arm IMbrella A extension and long-term observational study while patients treated with carboplatin and etoposide alone were not eligible. A total of 18 patients from the atezolizumab, carboplatin and etoposide arm of IMpower133 were enrolled in IMbrella A. Median follow-up was 59.4 months in the atezolizumab, carboplatin and etoposide arm (IMpower133 and IMbrella A; CCOD: March 16, 2023) vs. 26.4 months in the carboplatin and etoposide arm (IMpower133 only; CCOD: September 24, 2022). The 5-year overall survival (OS) rate in the atezolizumab, carboplatin and etoposide arm was 12% (IMpower133 and IMbrella A). At CCOD, 11 patients were still alive with the median age at baseline of 59 years while 4 patients had an ECOG PS of 1, 2 patients had baseline brain metastases and none had baseline liver metastases (15).

6.1.6 Efficacy – results per SKYSCRAPER-02

In January 2024 Rudin et al published the final progression free survival (PFS) and OS on SKYSCRAPER-02 (16). SKYSCRAPER-02 is a study of atezolizumab plus carboplatin and etoposide with or without tiragolumab in patients with 1L ES-SCLC. The tiragolumab arm did not meet its primary endpoint. Data from comparator arm will be used in the re-application as the comparator arm corresponds to the regime in question (atezolizumab, etoposide and carboplatin). Analysis included primary analysis set (PAS) and full analysis set (FAS).

In total 490 patients were randomized in the SKYSCRAPER-02. 247 patients were included in the FAS comparator arm and 201 patients in the PAS comparator arm. Median duration of follow-up was 13.9 months for FAS and 14.3 months for PAS. Median PFS was 5.6 months (5.4-5.9, 95% CI) in the PAS group and 5.4 months (4.5-5.7, 95% CI) in the FAS group. PFS rates at 6 and 12 months were 42.4% and 17.3%, respectively, in the PAS and 38.0% and 14.1%, respectively, in the FAS (16). In the final OS analysis, median duration of follow-up was 21.2 months. Median OS was 13.1 months (12.16-15.11, 95% CI) in the PAS group and 12.9 months (11.99-14.52, 95% CI) in the FAS group (16). Objective response rate (ORR) was 66.7% in PAS and 65.6% in FAS (16).

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

As the primary comparative analysis is a head-to-head analysis no comparison between studies are done. As supplementary data is used as single arm and to support the evidence on atezolizumab in combination with CP/EP.

7.1.2 Method of synthesis

As the primary analysis consist of a head-to-head study, no comparative analysis has been performed. Data on the control arm (atezolizumab plus CP/ET) from SKYSCRAPER-02 are presented and used as supplementary evidence.

7.1.3 Results from the comparative analysis

Table 9 Results from the comparative analysis of atezolizumab in combination with CP/ET vs. CP/ET for 1L ES-SCLC from IMpower133 (14).

Outcome measure	Atezo + CP/ET (N=201) (14)	CP/ET (N=202) (14)	Result
Median OS, months (95% CI) time point	12.3 (10.8-15.8)	10.3 (9.3-11.3)	2 months HR: 0.76 (0.60-0.95)
Median PFS, months (95% CI), time point	5.2 (4.4-5.6)	4.3 (4.2-4.5)	0.9 months HR: 0.77 (0.63-0.95)
ORR, % (95% CI), time point	60.2 (53.1 – 67.0)	64.4 (57.3-71.0)	4.2 %

Atezo – Atezolizumab, CP – carboplatin; ET - etoposide; OS – Overall survival; PFS- Progression free survival; ORR – objective response rate; HR – hazard rate; CI – confidence interval.

7.1.4 Efficacy – results per median OS

For IMpower133 Liu et al showed a median OS was 12.3 months (95% CI, 10.8 to 15.8) in the atezolizumab plus CP/ET arm and 10.3 months (95% CI, 9.3 to 11.3) in the placebo plus CP/ET arm (HR, 0.76; 95% CI, 0.60 to 0.95) (14). OS at 12 months demonstrated a survival increase of 12.9% in the atezolizumab plus CP/ET arm (51.9%) compared with the placebo plus CP/ET arm (39.0%). Similarly, at 18 months, 13.0% more patients were alive in the atezolizumab plus CP/ET arm (34.0%) than with placebo plus CP/ET (21.0%) (14).

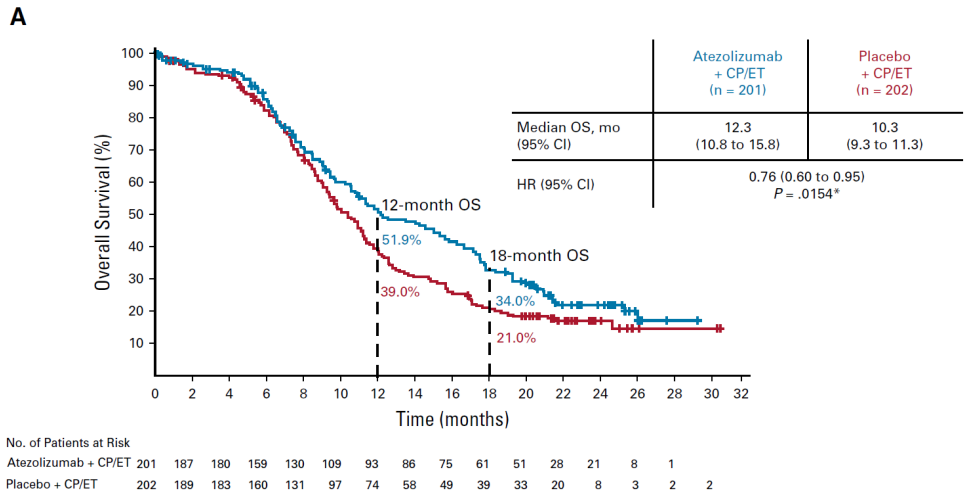
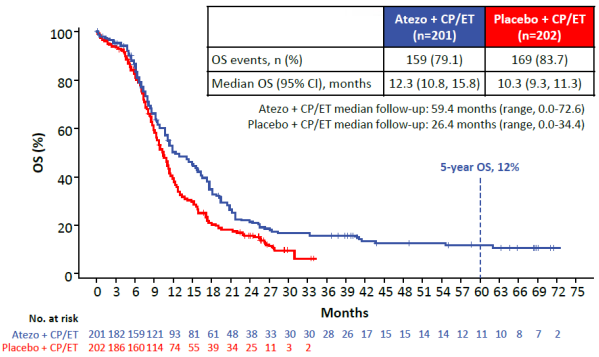


Figure 1 - Kaplan-Meier analysis of overall survival (OS) at the updated analysis of the intention-to-treat (ITT) population from IMpower133 (14).

*P value used for descriptive purposes only. [a]Hazard ratios (HRs) are nonstratified for patient subgroups and are stratified for the ITT population. CCOD: January 24, 2019. OS – overall survival; CP/ET - carboplatin plus etoposide.

In the IMpower133 extension study IMbrella A by Liu et al (15) median OS was reported the same as in the updated IMpower133 analysis (14). However, updated OS rates were reported at 24 months 22 % (95% CI, 16-28), 36 months 16 % (95% CI, 11-21), 48 months 13 % (95% CI, 8-18) and 60 months 12 % (95% CI, 7-17) (15).There are not reported OS rates for CP/ET in IMbrella A as rollover in IMbrella A was only permitted for atezolizumab plus CP/ET (15).



OS rate (95% CI), %	IMpower133 and IMbrella A Atezo + CP/ET (n=201)	IMpower133 only Placebo + CP/ET (n=202)
1-year	52% (45-59)	39% (32-46)
2-year	22% (16-28)	16% (11-21)
3-year	16% (11-21)	NE[a]
4-year	13% (8-18)	NE[a]
5-year	12% (7-17)	NE[a]

Figure 2 - Kaplan-Meier analysis of overall survival and OS rates from IMbrella A extension study (15).

CCOD: March 16, 2023. NE, not estimable. OS rates were NE in the control arm as rollover to IMbrella A was not permitted. OS – overall survival; CP/ET - carboplatin plus etoposide.

In the control arm of SKYSCRAPER-02 Rudin et al (16) reported that at the time of the interim OS analysis, 212 and 264 deaths had occurred in the PAS and FAS, respectively. OS data in the PAS were immature (HR, 1.04; 95% CI, 0.79 to 1.36; *P* = .7963; median OS, 13.6 months both treatment arms).

The final OS analysis was completed when 284 and 350 OS events had been observed in the PAS and FAS, respectively (CCOD: September 6, 2022). At this time point, 24 (9.7%) patients in the atezolizumab plus CP/ET arm remained on treatment in the FAS; median duration of follow-up was 21.2 months. Median OS at final OS analysis was the same in the PAS (13.1 months both arms; stratified HR, 1.14; 95% CI, 0.90 to 1.44; *P* = .2859), and similar in the FAS (12.9 months for the atezolizumab plus CP/ET arm; stratified HR, 1.09; 95% CI, 0.88 to 1.35; *P* = .4205). OS rates at 24 months were similar atezolizumab plus CP/ET arm in both the PAS (20% *v* 28%, respectively) and the FAS (21% *v* 26%, respectively) (16).

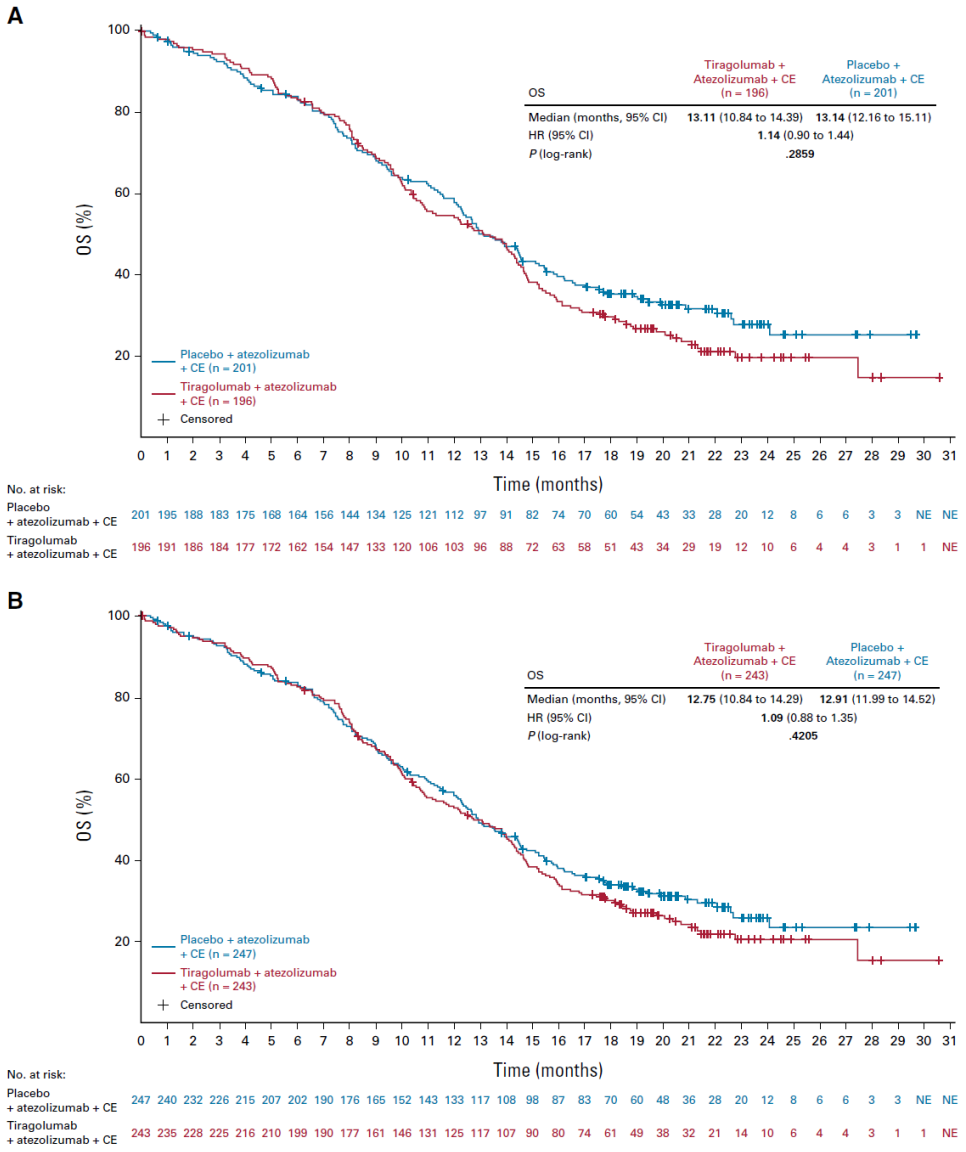


Figure 3 - OS in (A) the primary analysis set and (B) the full analysis set from SKYSCRAPER-02 (16).

CCOD: September 6, 2022. CE - carboplatin plus etoposide; HR - hazard ratio; NE - not evaluable; OS - overall survival.

7.1.5 Efficacy – results per median PFS

In IMpower133 Liu et al (14) reported median PFS in the ITT population at the updated analysis was 5.2 months (95% CI, 4.4 to 5.6) in the atezolizumab plus CP/ET arm and 4.3 months (95% CI, 4.2 to 4.5) in the placebo plus CP/ET arm (HR, 0.77; 95% CI, 0.63 to 0.95). At the updated analysis, 181 patients (90.0%) in the atezolizumab plus CP/ET arm and 194 patients (96.0%) in the placebo plus CP/ET arm had RECIST-defined disease progression. Disease progression occurred with the following patterns in the atezolizumab plus CP/ET and placebo plus CP/ET arms, respectively: 57.7% and 64.9% at existing lesions, 42.8% and 49.0% at new lesions, and 20.9% and 28.2% at both new and existing lesions. The patterns of progression in specific organs were generally similar between arms (14).

In SKYSCRAPER-02 Rudin et al (16), final analysis of PFS in the PAS was planned at the time of OS interim analysis, when 212 deaths had occurred. At the CCOD for the final PFS analysis (February 6, 2022), PFS events were experienced by 170 (84.6%) patients in the PAS in the atezolizumab plus CP/ET arm. In the FAS, 215 (87.0%) patients in the atezolizumab plus CP/ET arm experienced a PFS event. Median duration of follow-up was 13.9 months for the FAS and 14.3 months for the PAS. At this time point, 35 patients receiving atezolizumab plus CP/ET remained on treatment in the FAS. At the final analysis of PFS, the primary endpoint of PFS in the PAS was 5.6 months in the atezolizumab plus CP/ET arm. Median PFS in the FAS was similar to the PAS with 5.4 months in the atezolizumab plus CP/ET arm. In the PAS, PFS rates at 6 and 12 months were 42.4% and 17.3% with atezolizumab plus CP/ET arm. Corresponding PFS rates in the FAS were 38.0% and 14.1% with atezolizumab plus CP/ET arm (16).

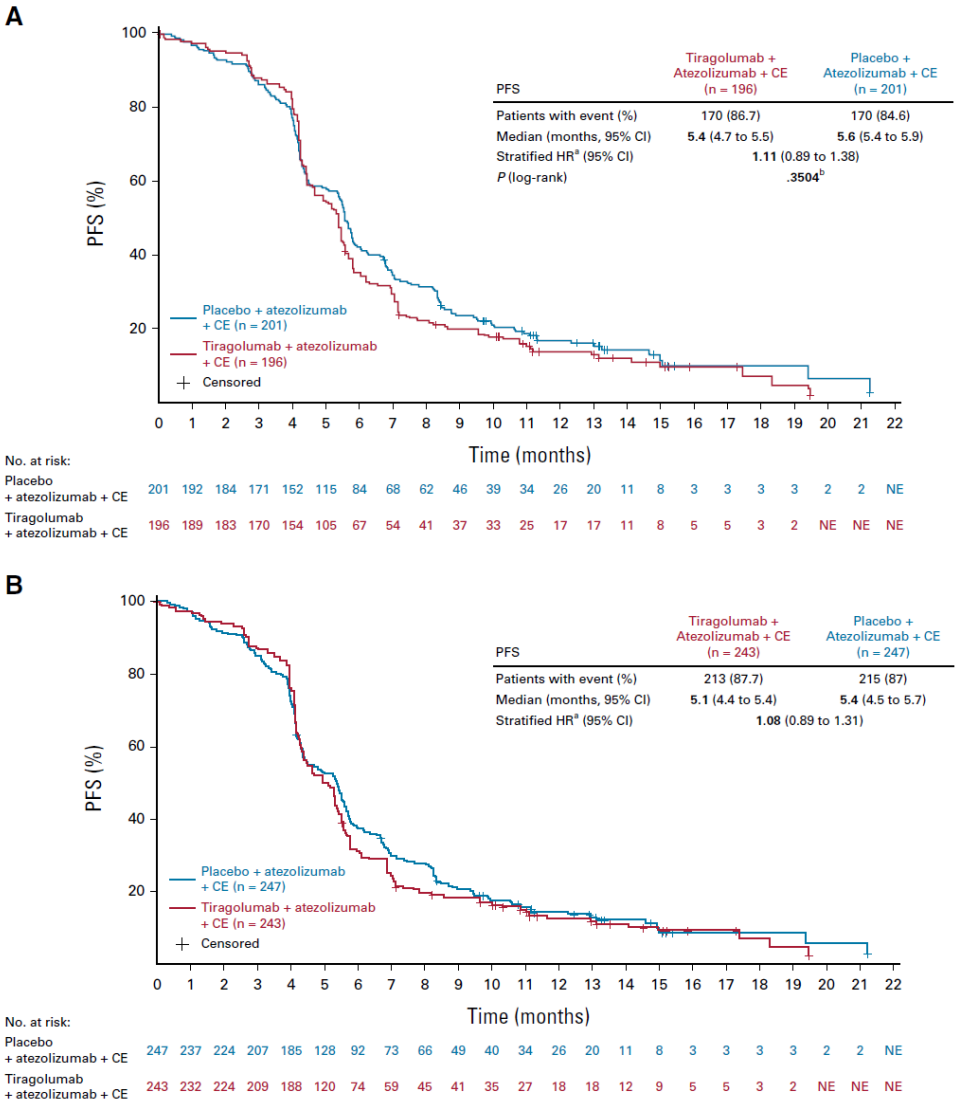


Figure 4 - PFS in (A) the primary analysis set and (B) the full analysis set from SKYSCRAPER-02 (16).

CCOD: February 6, 2022. CE, carboplatin plus etoposide; HR, hazard ratio; NE, not evaluable; PFS, progression-free survival. [a]Stratification factors are Eastern Cooperative Oncology Group and lactate dehydrogenase. [b]Statistical boundary: 0.001.

7.1.6 Efficacy – results per median ORR

In IMpower133 Liu et al (14) confirmed ORRs in the ITT population were 60.2% in the atezolizumab plus CP/ET arm (95% CI, 53.1 to 67.0) versus 64.4% (95% CI, 57.3 to 71.0; descriptive *P* = .3839) in the placebo plus CP/ET arm.

In SKYSCRAPER-02 Rudin et al (16) the PAS (CCOD: September 6, 2022), confirmed investigator-assessed ORR was 66.7% with atezolizumab plus CP/ET. CRs and PRs were observed in 1.5% and 65.2% of patients in atezolizumab plus CP/ET arm, respectively (16).

8. Modelling of efficacy in the health economic analysis

Not applicable in the 14-weeks process

9. Safety

9.1 Safety data from the clinical documentation

The safety population consists of patients with ES-SCLC from either intervention arm or comparator arm in the included studies. The safety data from IMpower133, is available in Table 10**,** whereas safety data for IMbrella A and SKYSCRAPER-02 is presented in text after the table**.** Safety data from the IMpower133 study originates from the initial pivotal study by Horn et al (19) and Liu et al. (14). Horn et al had CCOD at April 24, 2018. In IMpower133, the median duration of treatment was 4.7 months with Tecentriq (atezolizumab) and 4.1 months with placebo (14).

Table 10 Overview of safety events in studies IMpower133(19). The study had a start date of 07/06/2016, primary completion date: 24/04/2018 and study completion date: 0707/2022.

	Atezolizumab + CP/ET (N=198) Horn et al (19)	Placebo + CP/ET (N=196) Horn et al (19)	Difference, % (95 % CI)
Number of adverse events, n	2291	1919	372 (N/A)
Number and proportion of patients with ≥1 adverse events, n (%)	198 (100)	189 (96.4)	3.6 (N/A)
Number of serious adverse events*, n	74 (37.4)	68 (34.7)	2.7 (N/A)
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	45 (22.7)	37 (18.9)	3.8 (N/A)
Number of CTCAE grade ≥ 3 events, n	137 (69.2)	136 (69.4)	0.2 (N/A)
Number and proportion of patients with ≥ 1	115 (58.1)	113 (57.6)	0.5 (N/A)

	Atezolizumab + CP/ET (N=198) Horn et al (19)	Placebo + CP/ET (N=196) Horn et al (19)	Difference, % (95 % CI)
CTCAE grade ≥ 3 events§, n (%)			
Number of adverse reactions, n**	188 (94.9)	181 (92.3)	2.6 (N/A)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	22 (11.1)	6 (3.1)	8 (N/A)

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

** reported af treatment-related AEs

***Multiple occourences of the same AE in one patient were counted once as the highest grade for the preferred term

§ CTCAE v. 5.0 must be used if available.

IMbrella A: At CCOD, 11 patients were still alive with the median age at baseline of 59 years while 4 patients had an ECOG PS of 1, 2 patients had baseline brain metastases and none had baseline liver metastases. Only serious adverse events (AE) and AEs of special interest were collected in IMbrella A. Three serious AEs were observed (16.7%): diarrhea, pneumonia, and procedural pneumothorax.

SKYSCRAPER-02: 246 patients were in the safety population receiving atezolizumab, carboplatin and etoposide. All-grade AEs were reported for 245 (99.6%) patients. Grade 3/4 AEs were reported in 157 (63.8%) patients and 16 (6.5%) patients had grade 5 AEs. Treatment related AEs (TRAEs) grade 3/4 were reported in 227 (92.3%) patients and grade 5 TRAEs was observed in 5 (2.0 %). 23 (9.3%) patients had AEs leading to treatment withdrawal.

Table 11 Serious adverse events (CCOD April 24 2018) from IMpower133 (19)

Adverse events	Intervention (N=198)		Comparator (N=196)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	74 (37.4)	N/A	68 (34.7)	N/A

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

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

Not applicable in the 14-weeks process

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

Table 12 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
CORE 30 (QLQ-C30)) + Supplemental Lung Cancer Module : QLQ-LC13	IMpower133	The QLQ-C30 incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. Patient-reported outcomes were evaluated every 3 weeks during treatment (21)

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

Patient-reported outcomes (PROs) were evaluated as secondary and exploratory end points and measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire e Core 30 (QLQ-C30) version 37 and the supplemental lung cancer [Mansfield] module, QLQ-LC13.

The EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30) is a validated and reliable instrument specifically designed to assess the quality of life (QoL) of cancer patients. This tool is essential for evaluating the multidimensional impact of cancer and its treatment, making it a crucial component in health technology assessments (HTAs) for oncological interventions.

Key Features:

-Multidimensional Assessment: The QLQ-C30 encompasses 30 items that provide a comprehensive evaluation of quality of life across multiple dimensions, including physical, emotional, and social functioning, along with symptoms and side effects commonly associated with cancer and its treatment.

- Core Domains: The questionnaire is organized into five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, pain, and

nausea/vomiting), and a global health status/QoL scale. Additionally, it includes several single items addressing other symptoms and financial impact.

- Standardization and Validation: Developed by the EORTC Quality of Life Group, the QLQ-C30 has undergone extensive testing to ensure its reliability and validity across diverse cultural and linguistic populations. This standardization supports the comparability of results across different studies and settings.

- Wide Applicability: The QLQ-C30 is extensively used in clinical trials, observational studies, and routine clinical practice. It is instrumental in monitoring patient outcomes, informing treatment decisions, and enhancing the quality of patient care.

Scoring and Interpretation:

- Scoring System: Responses are rated on a Likert scale and then linearly transformed to a 0-100 scale. Higher scores on the functional scales and the global health status/QoL scale indicate better functioning and higher quality of life. Conversely, higher scores on the symptom scales reflect a greater burden of symptoms.

- Interpretation: The QLQ-C30 facilitates the identification of specific areas of patient distress, allows for the monitoring of changes over time, and enables the comparison of treatment effects on quality of life.

The EORTC QLQ-C30 is a critical tool in oncology for measuring patient-reported outcomes (PROs). It provides detailed insights into the impact of cancer and its treatments on patients' lives, thereby supporting the evaluation of new health technologies and interventions in terms of their benefits and effectiveness from the patient's perspective.

The EORTC QLQ-LC13 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13) is a specialized module designed to complement the EORTC QLQ-C30 by focusing specifically on issues relevant to lung cancer patients. This tool is integral in health technology assessments (HTAs) for interventions targeting lung cancer, providing detailed insights into the disease-specific impact on patients' quality of life.

Key Features:

- Disease-Specific Assessment: The QLQ-LC13 is tailored to address symptoms and treatment side effects that are particularly pertinent to lung cancer patients. It includes 13 items that delve into lung cancer-specific concerns.

- Focused Domains: This module evaluates symptoms such as cough, hemoptysis (coughing up blood), dyspnea (shortness of breath), site-specific pain, and the side effects of conventional chemo- and radiotherapy. It enhances the ability to assess the unique impact of lung cancer on patients.

- Standardization and Validation: Developed by the EORTC Quality of Life Group, the QLQ-LC13 has been rigorously tested to ensure its reliability and validity. It is

standardized for use across various cultural and linguistic groups, allowing for consistent and comparable data collection.

- Comprehensive Application: The QLQ-LC13 is used alongside the QLQ-C30 in clinical trials, observational studies, and routine clinical practice to provide a thorough evaluation of lung cancer-specific quality of life issues. This combined approach supports comprehensive patient monitoring and enhances the assessment of treatment efficacy.

Scoring and Interpretation:

- Scoring System: Each item is scored on a Likert scale, with responses transformed to a 0-100 scale. Higher scores indicate more severe symptoms or side effects. This scoring method facilitates the quantification and comparison of patient-reported outcomes.

- Interpretation: The QLQ-LC13 enables healthcare providers and researchers to identify specific areas where lung cancer patients experience the most distress. This detailed information supports the development of targeted interventions to alleviate symptoms and improve overall quality of life.

The EORTC QLQ-LC13, when used in conjunction with the QLQ-C30, offers a comprehensive evaluation of the quality of life in lung cancer patients. It is an essential instrument for assessing the patient-centered outcomes of new health technologies and treatments.

10.1.2 Data collection

QLQ-C30 and QLQ-LC13 assessments were completed on day 1 of each 21-day treatment cycle at scheduled study visits during treatment, and at 3 months and 6 months after treatment discontinuation. The PRO instruments, translated into the local language as required, were to be completed by patients on an electronic PRO device prior to administration of study treatment and prior to any other study assessments that might have biased their responses. Missing PRO scores were not imputed, but treated as random. Patients whose symptoms had not deteriorated before the last PRO assessment were censored at the date of the last PRO assessment. Patients with no baseline assessment or post-baseline assessments were censored at the date of randomization plus 1 day (20).

Table 13 Pattern of missing data and completion from IMpower133 (20).

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)

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

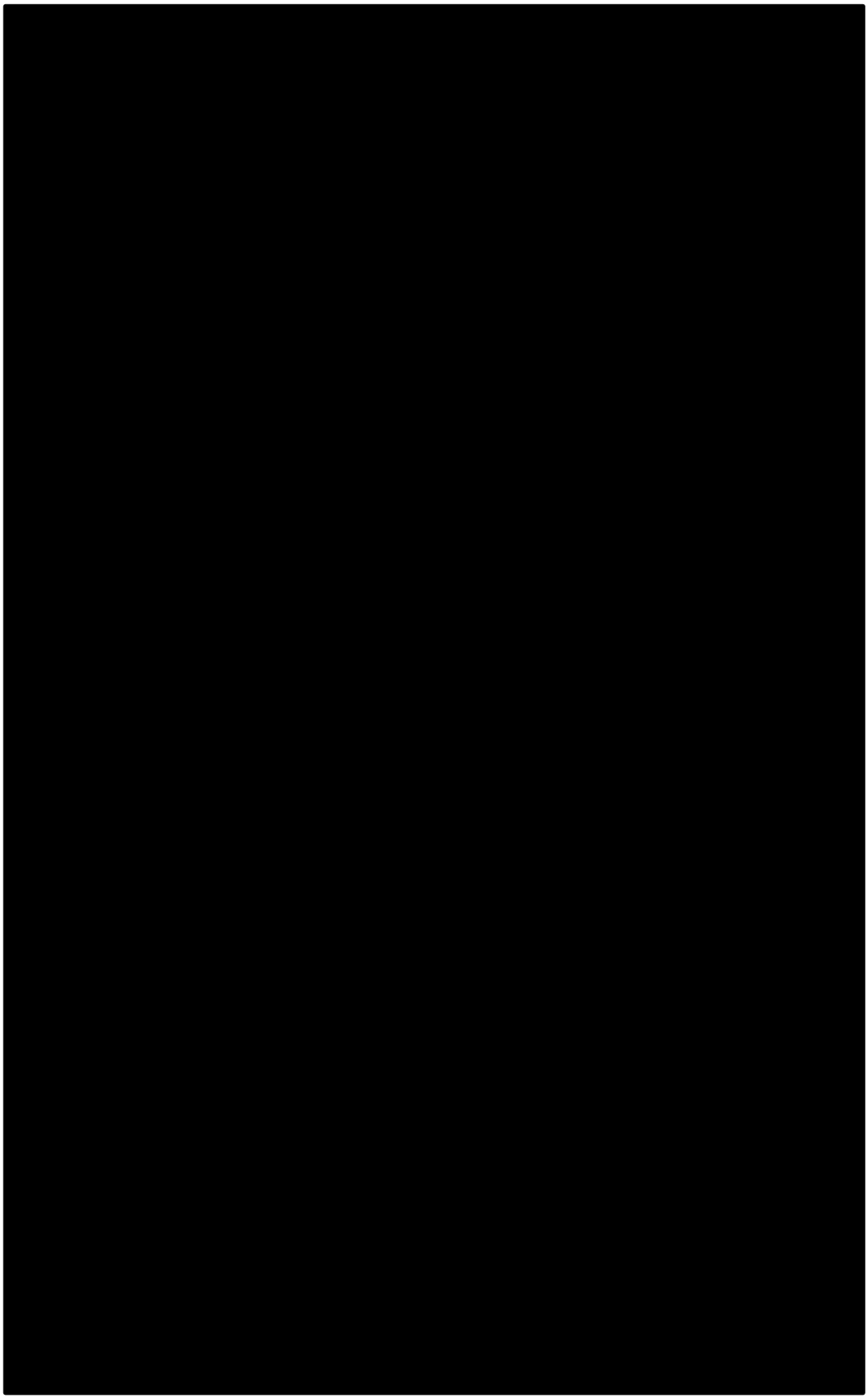
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				

10.1.3 HRQoL results

Table 14 HRQoL (EROTC QLQ-C30) summary statistics from IMpower133 (20).

	Intervention			Comparator		
	N	Mean (SD)	Change from baseline	N	Mean (SD)	Change from baseline

Intervention	Comparator



Intervention	Comparator
[redacted]	

Figure 5: Showing HRQoL during 54 weeks

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

Not applicable because no economic analysis is performed.

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

Not Applicable

11. Resource use and associated costs

Not applicable in the 14-weeks process

12. Results

Not applicable in the 14-weeks process

13. Budget impact model

Not applicable in the 14-weeks process

14. List of experts

As no health economic analysis was performed, no experts was interviewed for this application.

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Appendix A. Main characteristics of studies included

Table 15 Main characteristic of studies included

Trial name: IMpower133 (and extension study IMbrella A)	NCT number: NCT02763579 and NCT03148418
Objective	To demonstrate that adding atezolizumab (anti-programmed death-ligand 1 [PD-L1]) to carboplatin plus etoposide (CP/ET) for first-line (1L) treatment of extensive-stage small-cell lung cancer (ES-SCLC) results in significant improvement in overall survival (OS) and progression-free survival (PFS) versus placebo plus CP/ET
Publications – title, author, journal, year	Horn et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer, 2018. DOI: 10.1056/NEJMoa1809064 (19). Liu et al. Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133), 2021. DOI https://doi. org/10.1200/JCO.20. 01055 (14). Liu et al. Five-year survival in patients with ES-SCLC treated with atezolizumab in IMpower133: IMbrella A extension study results, 2023, World conference on lung cancer (15).
Study type and design	IMpower133: Completed, randomized, double-blind, phase I/III study, where patients with untreated ES-SCLC were randomly assigned 1:1 to receive four 21-day cycles of CP/ET with atezolizumab or placebo and then maintenance phase. IMbrella A: open-label, non-randomized, multicenter extension and long-term observational study. Only patients in survival follow up and from atezolizumab treatment arm in IMpower133 could be enrolled.
Sample size (n)	IMpower133: intervention, n = 201, placebo, n = 202. IMbrella A: n = 18
Main inclusion criteria	IMpower133: Eligible patients were adults with histologically or cytologically confirmed extensive-stage small-cell lung cancer as defined according to the Veterans Administration Lung Study Group staging system, measurable extensive stage small-cell lung cancer according to RECIST v 1.1, and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale, with higher numbers reflecting greater disability) who had not received previous systemic treatment for extensive-stage small-cell lung cancer. Patients with treated asymptomatic central nervous system metastases were eligible

Trial name: IMpower133 (and extension study IMbrella A)	NCT number: NCT02763579 and NCT03148418
	IMbrella A: If they continued to receive atezolizumab at IMpower133 study closure or were in survival follow-up.
Main exclusion criteria	IMpower133: Key exclusion criteria were a history of autoimmune disease and previous treatment with CD137 agonists or immune-checkpoint blockade therapies IMbrella A: if they were not in treatment with atezolizumab at IMpower133 study closure or were not in survival follow-up.
Intervention	IMpower133: receive four 21-day cycles of CP/ET with atezolizumab (1,200 mg IV, day 1) and then maintenance atezolizumab until unacceptable toxicity, disease progression, or loss of clinical benefit. 201 patients received intervention treatment. IMbrella A: Patients were still on atezolizumab treatment or in survival follow-up. 18 patients were included.
Comparator(s)	IMpower133: receive four 21-day cycles of CP/ET with placebo and then maintenance CP/ET and placebo until unacceptable toxicity, disease progression, or loss of clinical benefit. 202 patients received intervention treatment IMbrella A: None. The study was a follow-up one-armed extension study of atezolizumab.
Follow-up time	Median follow up time was 22.9 months. Median follow up for OS was 23.1 months (range, 0-29.5 months) in atezolizumab arm and 22.6 months (range, 0-30.7 months) in placebo arm.
Is the study used in the health economic model?	Not applicable due to 14 weeks application without health economic model.
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** <u>Primary efficacy endpoints:</u> The co-primary endpoints of this study are the following: • To evaluate the efficacy of atezolizumab + carpoplatin+etoposide compared with placebo + carboplatin + etoposide in the intent-to-treat (ITT) population as measured by investigator assessed progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors Carsion 1.1 (RECIST v1.1) • To evaluate the efficacy of atozelizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the ITT population as measured by overall survival (OS) <u>Safety endpoints</u>

- To evaluate the safety and tolerability of atezolizumab in combination with CP/ET compared with CP/ET

Other endpoints:

The secondary efficacy endpoints for this study are

- To evaluate the efficacy of atezolizumab + CP/ET compared with placebo + CP/ET in the ITT population as measured by investigator-assessed objective response rate (ORR) according to RECIST v1.1
- To evaluate the efficacy of atezolizumab + CP/ET compared with placebo + CP/ET in ITT population as measured by investigator-assessed duration of response (DOR) according to RECIST v1.1
- To evaluate the efficacy of atezolizumab + CP/ET compared with placebo + CP/ET in ITT population as measured by investigator-assessed time in response (TIR) according to RECIST v1.1
- To evaluate the PFS rate at 6 months and t 1 year in each treatment arm for the ITT population
- To evaluate the OS rate at 1 and 2 years in each treatment arm for the ITT population
- To evaluate the incidence and titers of anti-therapeutic antibodies (ATAs) against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy

The exploratory objectives for this study are:

- To evaluate the efficacy of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide in the PD-L1–selected population as measured by PFS, OS, ORR, and DOR
- To evaluate investigator-assessed disease control rate (DCR) according to RECIST v1.1 in the ITT population
- To evaluate investigator-assessed PFS, ORR, DCR, and DOR according to modified RECIST for the atezolizumab-containing treatment arm in the ITT population
- To evaluate the relationship between tumor biomarkers (including but not limited to PD-L1, programmed death-1 (PD-1), somatic mutations, and others), as defined by immunohistochemistry (IHC) or quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR), next

Trial name: IMpower133 (and extension study IMbrella A)	NCT number: NCT02763579 and NCT03148418
	generation sequencing (NGS), and/or other methods and measures of efficacy • To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue, blood, plasma and serum and their association with disease status, mechanisms of resistance, and/or response to study treatment • To evaluate and compare patient's health status as assessed by the EuroQoL 5 Dimensions 5-Level (EQ-5D-5L) questionnaire to generate utility scores for use in economic models for reimbursement • To determine the impact of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide as measured by change from baseline in patient-reported outcomes (PRO) of health-related quality of life, lung cancer–related symptoms, physical functioning, and health status as assessed by the EORTC QLQ-C30 and LC13 • To evaluate the impact of chemotherapy (both carboplatin and etoposide) on peripheral and tumor-specific T-cell populations during and after induction therapy and its relationship to efficacy and safety outcomes
Method of analysis	IMpower133: The two primary endpoints were investigator-assessed progression-free survival and overall survival in the intention-to-treat population. Kaplan–Meier methodology was used to estimate the probability of overall survival and progression-free survival, as well as to calculate the median time from randomization to death (for overall survival) and the median time from randomization to disease progression or death (for progression-free survival) for each group, and the Brookmeyer and Crowley method was used to construct the 95% confidence interval for the medians. A similar approach was used for the analysis of the duration of response. The hazard ratios and 95% confidence intervals for overall survival and progression-free survival were estimated with the use of a stratified Cox regression model, with the same stratification factors that were used in the stratified log-rank test
Subgroup analyses	To assess the consistency of the study results in pre-specified subgroups defined by demographics (e.g., age, sex, and race/ethnicity), baseline prognostic characteristics (e.g., ECOG performance status, smoking status, presence of brain metastases), and PD-L1 tumor expression status, the duration of PFS in these subgroups was examined. Summaries of PFS, OS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median PFS, was produced separately for each level of the categorical variables for the comparisons between treatment arms.

Trial name: IMpower133 (and extension study IMbrella A)	NCT number: NCT02763579 and NCT03148418
	The sample size of the study was determined by the analysis of OS. To detect an improvement of HR= 0.68 in OS using a log-rank test, approximately 298 deaths in the ITT population was required to achieve 90% power at a two-sided significance level of 0.045.
Other relevant information	N/A

Trial name: SKYSCRAPER-02	NCT number: NCT04256421
Objective	This study will evaluate the efficacy of tiragolumab plus atezolizumab and carboplatin and etoposide (CE) compared with placebo plus atezolizumab and CE in participants with chemotherapy-naive extensive-stage small cell lung cancer (ES-SCLC).
Publications – title, author, journal, year	SKYSCRAPER-02: Tiragolumab in Combination With Atezolizumab Plus Chemotherapy in Untreated Extensive-Stage Small-Cell Lung Cancer; Rudin C et al; J Clin Oncol; jan 2024 (16).
Study type and design	This is a randomized, Phase III, global, multicenter, double-blinded, placebo-controlled study designed to evaluate the safety and efficacy of tiragolumab in combination with atezolizumab and C/E compared with treatment with placebo in combination with atezolizumab and C/E in patients who are chemotherapy-naive ES-SCLC Eligible participants will be stratified by Eastern Cooperative Oncology Group (ECOG) Performance Status (0 vs. 1), LDH (</= upper limit of normal [ULN] vs. > ULN), and presence or history of brain metastasis (yes vs. no) and randomly assigned in a 1:1 ratio to either of the two treatment arms.
Sample size (n)	Overall, 490 patients were enrolled into the study and were randomly assigned, FAS This is in accordance with the protocol, having minimum FAS= 470, PAS=400
Main inclusion criteria	Histologically or cytologically confirmed extensive-stage small cell lung cancer (ES-SCLC); No prior systemic treatment for ES-SCLC; Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1; Measurable disease, as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1); Adequate hematologic and end-organ function; Treatment-free for at least 6 months since last chemo/radiotherapy, among those treated (with curative intent) with prior chemo/radiotherapy for limited-stage SCLC.
Main exclusion criteria	Symptomatic or actively progressing central nervous system (CNS) metastases; Malignancies other than small cell lung cancer (SCLC) within 5 years prior to randomization, with the exception of those with a

Trial name: IMpower133 (and extension study IMbrella A)	NCT number: NCT02763579 and NCT03148418
	negligible risk of metastasis or death treated with expected curative outcome; Active or history of autoimmune disease or immune deficiency; History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan; Positive test result for human immunodeficiency virus (HIV); Active hepatitis B or hepatitis C; Severe infection at the time of randomization; Treatment with any other investigational agent within 28 days prior to initiation of study treatment; Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-cytotoxic T lymphocyte-associated protein 4 (anti-CTLA-4), anti-TIGIT, anti-PD-1, and anti-PD-L1 therapeutic antibodies; Treatment with systemic immunostimulatory agents within 4 weeks or 5 drug elimination half-lives prior to randomization.
Intervention	Only study data from the comparator arm is used in this application. Tiragolumab in combination Tecentriq (atezolizumab), carboplatin and etoposide. Dosing: four 21-day cycles of IV Tiragolumab and IV atezolizumab (1,200 mg once on day 1 of each cycle) plus IV carboplatin (area under the curve: 5 mg/mL/minute once on day 1 of each cycle for 4 cycles) and IV etoposide (100 mg/m2 once on days 1,2, and 3 of each cycle for 4 cycles). Dosing schedule: followed by maintenance Tiragolumab and atezolizumab in 21-day cycles until radiographic PD per RECIST version 1.1, or for as long as patients experienced clinical benefit without unacceptable toxicity as assessed by the investigator. N = 201
Comparator(s)	Tecentriq (atezolizumab) in combination with carboplatin and etoposide. Dosing: four 21-day cycles of IV atezolizumab (1,200 mg once on day 1 of each cycle) plus IV carboplatin (area under the curve: 5 mg/mL/minute once on day 1 of each cycle for 4 cycles) and IV etoposide (100 mg/m2 once on days 1,2, and 3 of each cycle for 4 cycles). Dosing schedule: followed by maintenance atezolizumab in 21-day cycles until radiographic PD per RECIST version 1.1, or for as long as patients experienced clinical benefit without unacceptable toxicity as assessed by the investigator. N = 202
Follow-up time	Median duration on follow up, 14.3 months (Primary analysis set) and 13.9 months (Full analysis set)

Trial name: IMpower133 (and extension study IMbrella A)	NCT number: NCT02763579 and NCT03148418
Is the study used in the health economic model?	Not applicable due to 14 weeks application without health economic model.
Primary, secondary and exploratory endpoints	The primary efficacy objective for the study is to evaluate the efficacy of tiragolumab plus atezolizumab and CE compared with placebo plus atezolizumab and CE in patients with untreated ES-SCLC on the basis of the following co-primary endpoints: **Endpoints included in this application:** • PFS after randomization, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first in patients who are randomly assigned without presence or history of brain metastases at baseline (primary analysis set [PAS]) • OS after randomization, defined as the time from randomization to death from any cause in the PAS **Other endpoints:** The secondary efficacy objective for this study is to evaluate the efficacy of tiragolumab plus atezolizumab and CE compared with placebo plus atezolizumab and CE on the basis of the following endpoints: • PFS in the FAS • OS in the FAS • Confirmed ORR, defined as the proportion of patients with a confirmed objective response (i.e., complete response [CR] or PR on two consecutive occasions ≥ 4 weeks apart), as determined by the investigator according to RECIST v1.1 in the PAS and the FAS who have measurable disease at baseline • DOR for patients with confirmed objective response, defined as the time from the first occurrence of a documented, confirmed objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first in the PAS and the FAS • PFS rates at 6 months and at 12 months in the PAS and the FAS • OS rates at 12 months and 24 months in the PAS and the FAS • Time to confirmed deterioration (TTCD) in patient-reported physical functioning and global health status/quality of life (GHS/QoL), as measured by the European Organisation for

Trial name: IMpower133 (and extension study IMbrella A)	NCT number: NCT02763579 and NCT03148418
	the Research and Treatment of Cancer (EORTC) Quality of Life–Core 30 Questionnaire (QLQ-C30) in the PAS and the FAS **Safety objectives:** The safety objective for this study is to evaluate the safety of tiragolumab plus atezolizumab and CE compared with placebo plus atezolizumab and CE on the basis of the following endpoints: • Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0 • Severity for CRS will also be determined according to the American Society for Transplantation and Cellular Therapy (ASTCT) CRS consensus grading scale The exploratory safety objective for this study is to evaluate the safety of tiragolumab plus atezolizumab and CE compared with placebo plus atezolizumab and CE from the patient's perspective, on the basis of the following endpoints: • Frequency, severity, interference, and/or presence of selected symptomatic treatment toxicities, as determined by the NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) • Change from baseline in symptomatic treatment toxicities, as assessed through use of the PRO-CTCAE • Frequency of patients' response of the degree they are troubled with treatment symptoms, as assessed through use of the single-item EORTC Item List 46 (IL46)
Method of analysis	Method of analysis were intention to treat (ITT). Survival analyses were performed in the PAS and FAS, with patients grouped according to assigned treatment. Safety analyses were performed according to treatment received. To control the overall type 1 error rate at 0.05 (two-sided), end points were tested hierarchically. A two-sided α of .001 and .049 was allocated to PFS and OS in the PAS, respectively. If PFS in the PAS was statistically significant at the two-sided α level of .001, OS in the PAS was tested at α two-sided a level of .05. If the OS benefit in the PAS was statistically significant, PFS and OS were tested in the FAS, using the same a-allocation ratio (1:49) and an α-recycle strategy. A sample size of approximately 400 patients was targeted for the PAS, assuming a 15% prevalence of presence or history of brain metastases at baseline. It was estimated that approximately 470 patients would be randomly assigned within the study. The primary analysis of the primary efficacy end point, PFS in the PAS, was planned at the time of the OS efficacy interim analysis when

Trial name: IMpower133 (and extension study IMbrella A)	NCT number: NCT02763579 and NCT03148418
	approximately 202 deaths had been observed in the PAS. At the time of the primary analysis of PFS, it was estimated that approximately 300 PFS events would have been observed to provide 96% power for a target PFS hazard ratio (HR) of 0.56 at a two-sided significance level of .001. This would assume a median PFS of 5.2 months in the placebo plus atezolizumab and CE arm and 9.2 months in the tiragolumab plus atezolizumab and CE arm. There was no planned interim analysis for PFS. The final analysis of the primary end point, OS in the PAS, was planned for when approximately 288 deaths had been observed in the PAS. This would provide 85% power to detect a target OS HR of 0.70 at a two-sided significance level of .049, assuming a median OS of 12.3 months in the placebo plus atezolizumab and CE arm and 17.6 months in the tiragolumab plus atezolizumab and CE arm. One efficacy interim and one final analysis of OS was planned. To control the type I error, stopping boundaries of these analyses were computed with the Lan-DeMets approximation to the O'Brien-Fleming.16 The stopping boundaries for the efficacy interim and final OS analyses are provided in the Data Supplement. The stratified log-rank test was used to compare PFS and OS between treatment arms; the HR for PFS and OS was estimated using a stratified Cox proportional hazards model. Kaplan-Meier methodology was used to estimate median PFS and OS, and the Brookmeyer-Crowley method was used to construct 95% CIs.
Subgroup analyses	Not applicable
Other relevant information	

Appendix B. Efficacy results per study

Results per study

Efficacy results illustrated for IMpower133

Table 16 Results from IMpower133

Results of IMpower133 (NCT02763579)											
				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**		
Updated OS - Median	Tecentriq(atezolizumab)	201	12.3 (10.8 – 15.8) months	2.0	N/A	N/A	HR: 0.70	0.54-0.91	0.007	The median survival is based on the Kaplan-Meier estimator at the updated analysis of the intention-to-treat population. The HR is based on a Cox proportional hazards model	Horn et al (19)
	Placebo	202	10.3 (9.3-11.3) months								
Investigator assessed PFS per RECIST version 1.1 (RECIST 1.1) in the intention-to-treat (ITT)	Tecentriq (atezolizumab)	201	5.2 months	0.9	N/A	N/A	HR: 0.77	0.62-0.96	0.02	Kaplan-Meier estimator was used to calculate the median time from randomization to disease progression or death in the intention-to-treat population. The HR is based on a Cox proportional hazards model	Horn et al (19)
	Placebo	202	4.3 months								

Results of IMpower133 (NCT02763579)											
				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		
population – Median											
EORTC QLQ-C30 - Global Health Status	Tecentriq (atezolizumab) - Baseline	179	51.63 (48.3 to 54.9)	2.1	−2.72 to 6.88	0.39	NA	NA	NA	The absolute difference in effect is estimated using a two-sided t-test.	Horn et al (19) and Mansfield (20)
	Placebo - Baseline	175	53.71 (50.2 to 57.2)								
	Tecentriq (atezolizumab) – Week 27	55	65.30 (59.6 to 70.1)	3.42	-12.55 to 5.70	0.46	NA	NA	NA		
	Placebo – Week 27	40	61.88 (54.80 to 68.97)								
	Tecentriq (atezolizumab) – Week 54	17	62.75 (53.66 to 71.84	0.63	-17.02 to 15.76	0.94	NA	NA	NA		
	Placebo – Week 54	11	62.12 (48.66 to 75.58)								

Results of IMpower133 (NCT02763579)												
				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**		
ORR	Tecentriq (atezolizumab)		60.2% (53.1-67.0)	-4.2%						Proportion of patients with an objective response, either CR or PR Clopper-Pearson method for 95% CI of response rates 95% CI for the difference in ORRs between the two treatment arms was estimated using the normal approximation to the binomial distribution method	Liu et al (14)
	Placebo		64.4% (57.3-71.0)								

*P value used for descriptive purpose

Appendix C. Comparative analysis of efficacy

[For meta-analyses, the table below can be used. For any type of comparative analysis (i.e. paired indirect comparison, network meta-analysis or MAIC analysis), describe the methodology and the results here in an appropriate format (text, tables and/or figures).]

Table 17 Comparative analysis of the IMpower133 study comparing Tecentriq (atezolizumab) to CB/ET for patients with ES-SCLC (based on the clinical study report data)

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		
Median overall survival Time from randomization to death from any cause	1	2	Not available	Not available	HR: 0.70	0.54–0.91	0.007	Kaplan-Meier methodology, stratified log-rank test and stratified Cox regression model. Stratification factors should be the same as for randomization including: sex [male vs. female], ECOG performance status [0 vs.1], and brain metastasis [Yes vs. No], as recorded in the IxRS, unless at least one stratum had less than 10 events. If that happened, the stratification factor which contained the level with the smallest number of patients was removed from the stratified analyses until there was no stratum with less than 10 events	Not applicable

[redacted]

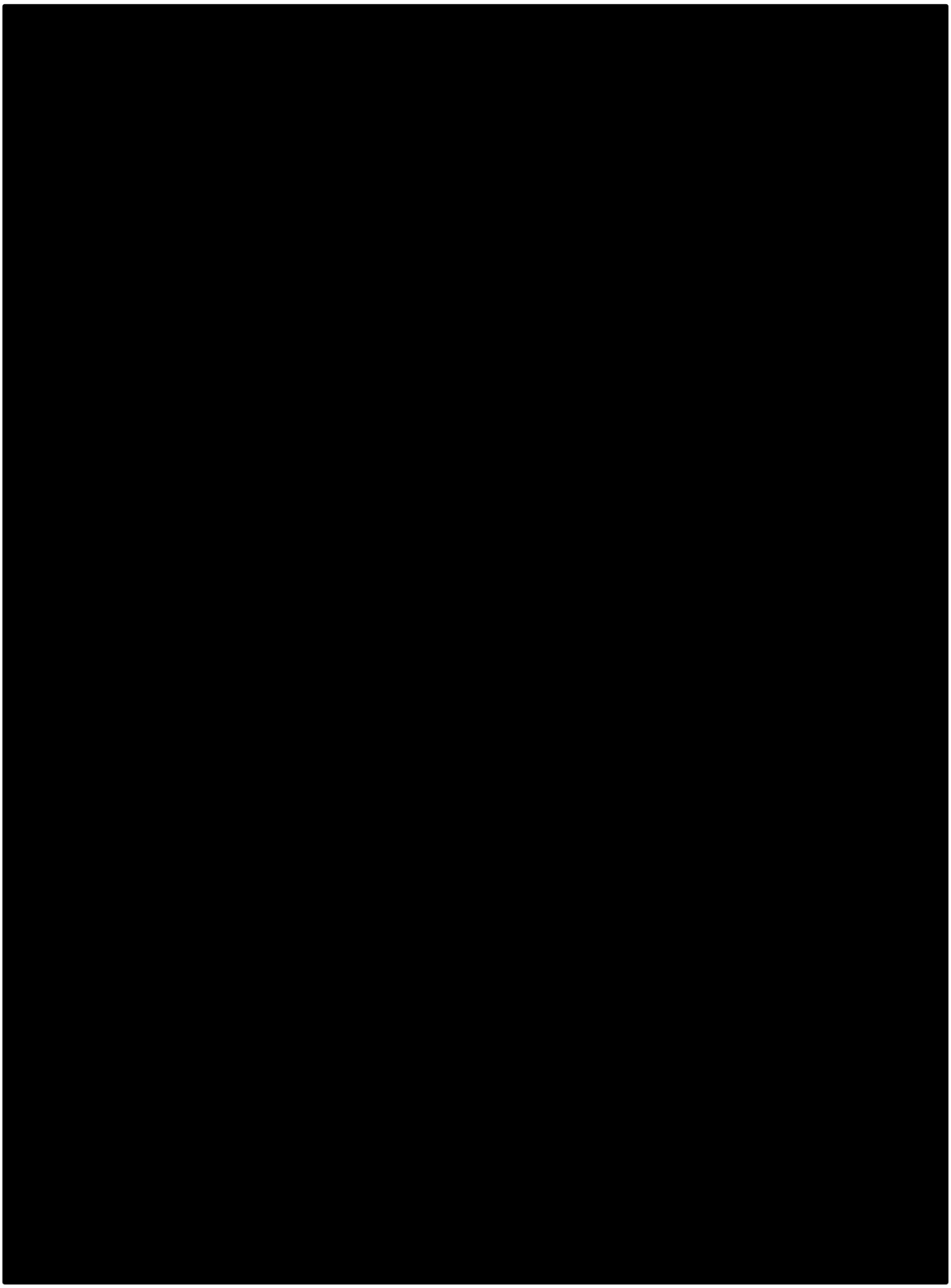
Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		
2-year OS landmark timepoint (Liu et al (15))	1	6 %	N/A	N/A	N/A		N/A	N/A	Not applicable
PFS per RECIST v1.1 by investigator Time from randomization to first documented PD or death from any cause, whichever occurred first	1	0.9 months	N/A	N/A	HR: 0.77	0.62-0.96	0.017	Same method as for OS co-primary endpoint	Not applicable
[redacted]									
Objective response rate (ORR) (Liu et al (14))	1	-4.2%	N/A	N/A	HR: 0.67	(0.51-0.88)	0.0037		Not applicable

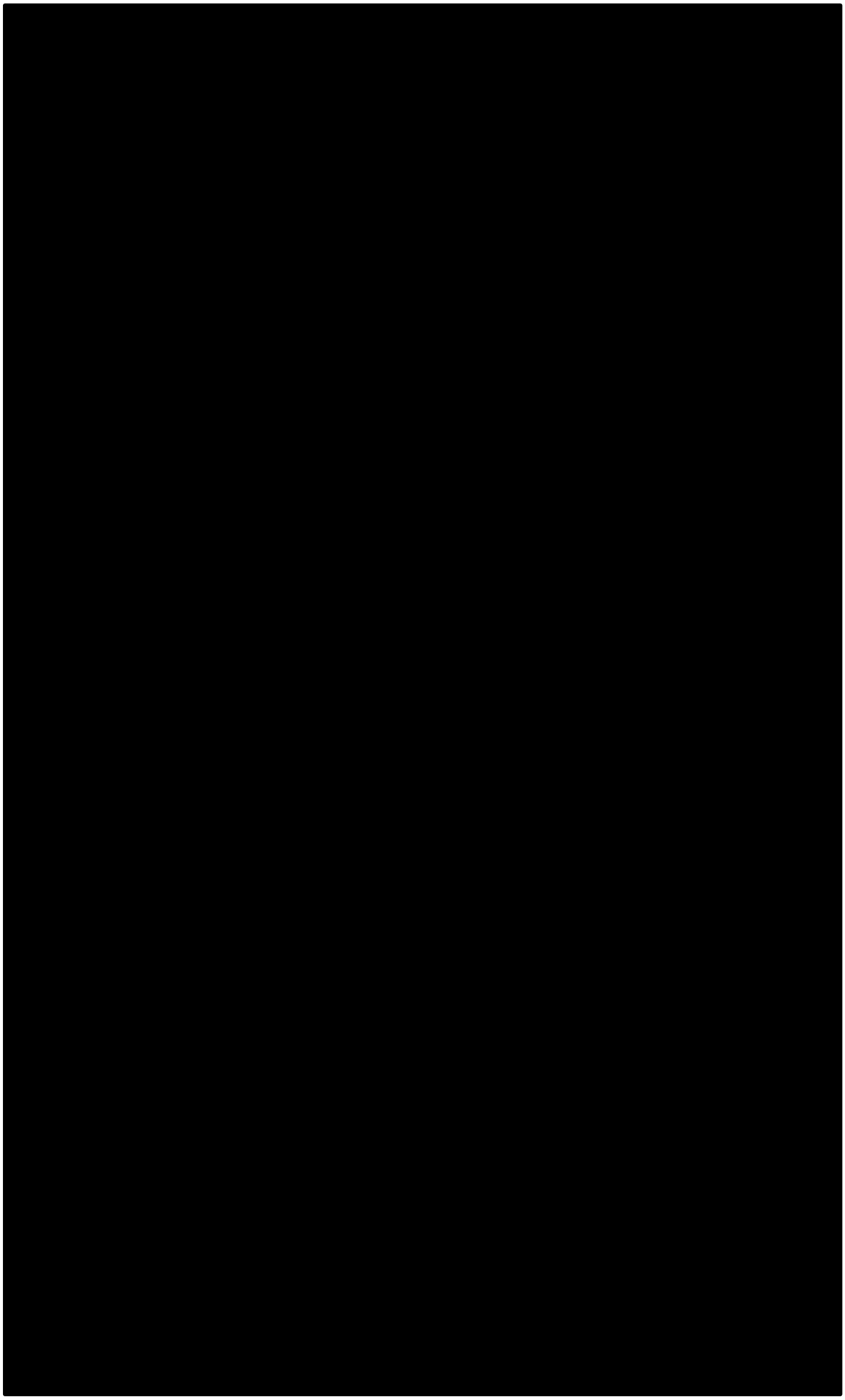
Appendix D. Extrapolation

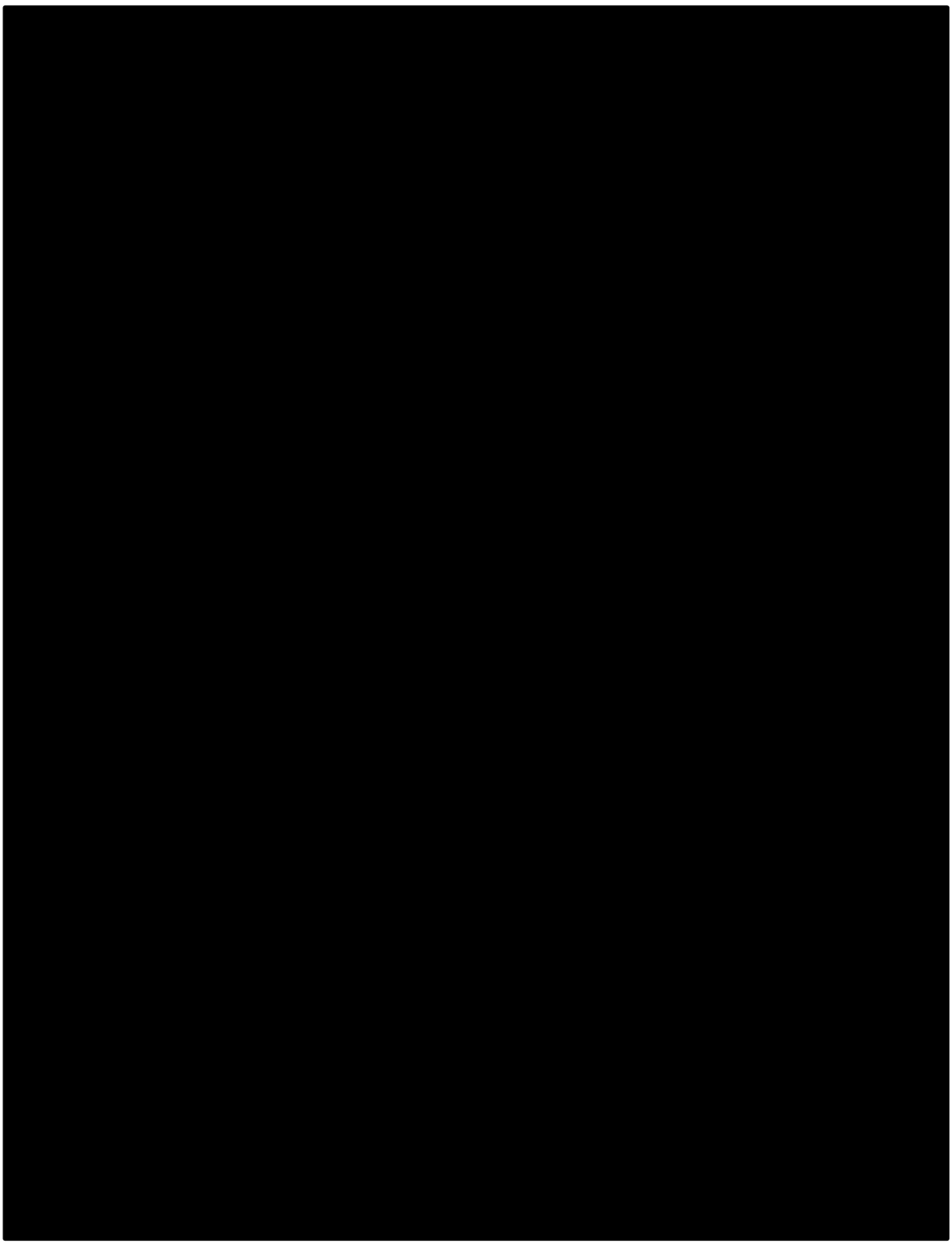
As no health economic analysis was performed for this application, the extrapolation appendix was not included.

Appendix E. Serious adverse events

This appendix contains all serious adverse events in the IMpower133 study. Data originates from the clinical study report on atezolizumab.

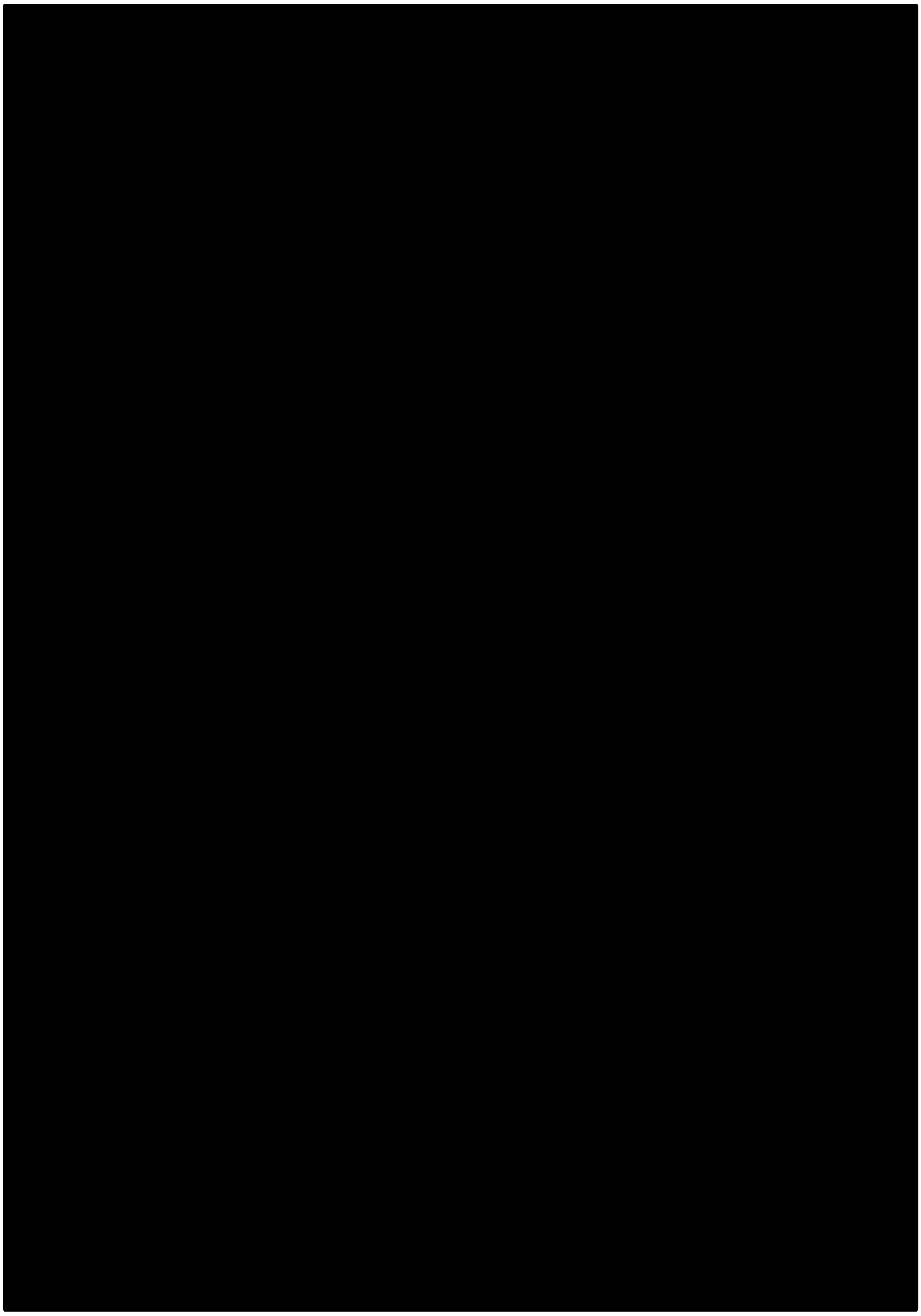






Appendix F. Health-related quality of life

Figure 6: EORTC QLQ-C30 subdomains



Appendix G. Literature searches for the clinical assessment

No literature search was made for atezolizumab in combination with carboplatin and etoposide.

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

No literature search on HRQoL was made for atezolizumab in combination with carboplatin and etoposide

Appendix I. 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 PD-L1 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 J. Other indications that have been evaluated by the DMC

Overview of indications evaluated by DMC on Tecentriq (atezolizumab)

Table 18 Overview of indications evaluated by DMC on Tecentriq (atezolizumab)

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

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