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Atezolizumab (small cell lung cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Atezolizumab (kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 January 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CI_u	upper limit of confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire Lung Cancer 13
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire Core 30
EQ-5D	European Quality of Life-5 Dimensions
ES-SCLC	Extensive Stage Small Cell Lung Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IPD	individual patient data
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug atezolizumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 7 October 2019.

Research question

The aim of the present report is the assessment of the added benefit of atezolizumab in combination with carboplatin and etoposide (hereinafter referred to as atezolizumab + carboplatin + etoposide) in comparison with the appropriate comparator therapy (ACT) in adult patients as first-line treatment of advanced small cell lung cancer (Extensive Stage Small Cell Lung Cancer, ES-SCLC).

The G-BA's specification of the ACT resulted in one research question, which is presented in the following Table 2.

Table 2: Research question of the benefit assessment of atezolizumab + carboplatin + etoposide

Research question	Therapeutic indication[a]	ACT[b, c]
1	Extensive Stage Small Cell Lung Cancer (ES-SCLC)	**Carboplatin + etoposide** or cisplatin + etoposide

a. For the present therapeutic indication, the G-BA assumed patients to have stage IV SCLC (staging according to the IASLC and the UICC). Moreover, the G-BA assumed that prophylactic radiation of the skull was performed and documented in both study arms. Regular monitoring for brain metastases by means of imaging techniques is necessary for patients who received no prophylactic radiation of the skull.
b. It is assumed that platinum-based first-line chemotherapy had been completed by the time maintenance treatment with atezolizumab monotherapy was initiated. According to available evidence, performance of maintenance treatment after initial response to the first-line treatment presents no standard in the treatment of ES-SCLC, because a benefit regarding long-term survival has not been demonstrated to date. Therefore, it is assumed that BSC was available to the patients in the control arm. BSC is understood as the therapy that ensures the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.
c. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

ACT: appropriate comparator therapy; BSC: best supportive care; ES SCLC: Extensive Stage Small Cell Lung Cancer; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; UICC: Union for International Cancer Control

The company followed the G-BA's specification of the ACT and chose carboplatin + etoposide from the options presented.

The assessment was made by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

Results

One relevant study (IMpower133) was available for the benefit assessment.

Study characteristics

The IMpower133 study is a double-blind, placebo-controlled RCT on the comparison of atezolizumab in combination with carboplatin and etoposide versus carboplatin + etoposide in the present therapeutic indication. The study included adult patients with ES-SCLC who had not yet received systemic treatment against ES-SCLC. The general condition of the patients had to correspond to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Patients with brain metastases could be included if these had been treated and were asymptomatic at the time point of inclusion. Therefore, there are no data for patients with untreated or symptomatic brain metastases and for patients with ECOG PS ≥ 2. Worldwide, a total of 403 patients were randomly assigned in a ratio of 1:1.

Patients received atezolizumab or placebo for a total of 4 21-day cycles, each followed by carboplatin and etoposide. Following the 4th cycle, treatment with atezolizumab or placebo as maintenance therapy was continued and treatment with carboplatin and etoposide was terminated. Application of the drugs was largely in accordance with the specifications of the Summary of Product Characteristics (SPC) and guidelines.

Co-primary outcomes of the Impower133 study were “progression-free survival (PFS)” and “overall survival”. Patient-relevant secondary outcomes were outcomes of the categories “morbidity” (symptoms, health status), “health-related quality of life” and “side effects”.

Cohort in China

According to the company, additional patients from China (N = 100) and Taiwan (N = 10) were recruited for the purpose of an approval in China. According to the study protocol, this was done after completion of the recruitment phase of the global cohort into a separate cohort. The patients were treated according to the same study protocol and statistical analysis plan (SAP) as the global study population, but the data were analysed and presented separately.

Consequences of missing analyses on the cohort in China

The company did not use the results of the cohort in China for the derivation of an added benefit, but presented them as supplementary information in a separate section in Module 4 A. In addition to regulatory reasons, the company justified this with differences in characteristics at the start of the study such as ethnic origin, age group distribution, gender distribution, ECOG PS, and smoking status.

However, the patients of the cohort in China represent a relevant subpopulation of the IMpower133 study and are included in the present benefit assessment. An effect modification by the characteristic "family origin" was not shown for the outcomes on efficacy in the subgroup analyses performed by the company. Where possible, a meta-analysis of the results from both cohorts is conducted.

For some outcomes, a meta-analysis of the two cohorts could not be performed due to missing data or analyses and a summarizing assessment of the added benefit was thus impossible.

Data cut-offs

Several data cut-offs are available for the analysis of the Impower133 study. For the outcome "overall survival", the present assessment is based on the second data cut-off in both cohorts (24 January 2019). The data cut-offs of 24 April 2018 (global cohort) and of 29 October 2019 (cohort in China) were used for the outcomes "morbidity" and "health-related quality of life", the data cut-offs of 24 April 2018 (global cohort) and 24 January 2019 (cohort in China) were used for the outcomes on side effects.

Risk of bias

The risk of bias at study level was rated as low.

The risk of bias of the results on the outcome "overall survival" was rated as low. However, adequate assessment of the outcome "overall survival" is impossible, since the company only presented all analyses for a part of the relevant population.

For the outcomes on "symptoms" and "health-related quality of life" as well as "serious adverse events (SAEs)" and "severe AEs" (Common Terminology Criteria of Adverse Events [CTCAE] grade 3 and 4)", the risk of bias of the results was rated as high due to incomplete observations for potentially informative reasons.

The risk of bias of the results on the outcome "discontinuation due to AEs" was rated as low. However, a restricted certainty of results was assumed for this outcome.

Moreover, the outcomes "immune-related AEs", "immune-related SAEs" and "immune-related severe AEs" were used for the assessment. For the results on these outcomes, the risk of bias was assessed retrospectively and also rated as high.

Mortality

Overall survival

For the outcome "overall survival", the meta-analysis of the results of both cohorts showed a statistically significant difference in favour of atezolizumab + carboplatin + etoposide. Thereby, the upper limit of the confidence interval (CI_u) was 0.99 and thus very close to the zero effect. However, an effect modification by the characteristic "age" ($p = 0.048$) was shown in the global cohort. A statistically significant advantage of atezolizumab + carboplatin + etoposide with the

extent “major” was only found for the subgroup of patients aged 65 years and older. Since subgroup analyses are missing for the cohort in China and also for both cohorts together, it is unclear in how far the inclusion of the cohort in China affects the results. Thus, adequate assessment of the added benefit cannot be made for the outcome “overall survival”.

Morbidity and health-related quality of life

There were no statistically significant group differences for the outcomes on symptoms, the outcome “health status” and the outcomes on the health-related quality of life. There were no usable data for cognitive functioning. This resulted in no hint of an added benefit of atezolizumab in combination with carboplatin and etoposide in comparison with carboplatin and etoposide for any of these outcomes. An added benefit is therefore not proven.

Side effects

SAEs, severe AEs (CTCAE grade 3 and 4)

No statistically significant difference between the treatment groups was shown for the outcomes “SAEs” and “severe AEs (CTCAE grade 3 or 4)”. This resulted in no hint of greater or lesser harm from atezolizumab in combination with carboplatin and etoposide in comparison with carboplatin and etoposide for the outcomes “SAEs” and “severe AEs (CTCAE grade 3 and 4)”. Greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference between the treatment groups to the disadvantage of atezolizumab in combination with carboplatin and etoposide was shown in both cohorts for the outcome “discontinuation due to AEs”. This resulted in a hint of greater harm from atezolizumab in combination with carboplatin and etoposide in comparison with carboplatin and etoposide for this outcome.

Specific AEs

Immune-related AEs, immune-related SAEs, immune-related severe AEs (CTCAE grade 3 and 4)

A statistically significant difference between the treatment groups to the disadvantage of atezolizumab in combination with carboplatin and etoposide was shown for each of the outcomes “immune-related AEs”, “immune-related SAEs” and “immune-related severe AEs”. This resulted in a hint of greater harm from atezolizumab in combination with carboplatin and etoposide in comparison with carboplatin and etoposide for each of these outcomes.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of the added benefit of the drug atezolizumab in combination with carboplatin and etoposide versus the ACT is assessed as follows:

Table 3 presents a summary of the probability and extent of the added benefit of atezolizumab in combination with carboplatin and etoposide.

Table 3: Atezolizumab in combination with carboplatin and etoposide – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Extensive Stage Small Cell Lung Cancer [b]	**Etoposide + carboplatin** or etoposide + cisplatin	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. The IMpower133 study only included patients with ECOG PS of 0 or 1 and with treated and asymptomatic brain metastases. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or with untreated or symptomatic brain metastases.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

Based on the available analyses, the overall consideration shows negative effects for the outcomes "discontinuation due to AEs", "immune-related AEs", "immune-related severe AEs" and "immune-related SAEs".

An adequate conclusion on the added benefit cannot be made since usable analyses on overall survival are not available for the total population of IMpower133 (global cohort + cohort in China).

In summary, an added benefit of atezolizumab in combination with carboplatin and etoposide in comparison with carboplatin and etoposide has not been proven for adult patients with ES-SCLC.

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

2.2 Research question

The aim of the present report is the assessment of the added benefit of atezolizumab in combination with carboplatin and etoposide (hereinafter referred to as atezolizumab + carboplatin + etoposide) in comparison with the ACT as first-line treatment for adult patients with ES-SCLC.

The G-BA's specification of the ACT resulted in one research question, which is presented in the following Table 4.

Table 4: Research questions of the benefit assessment of atezolizumab + carboplatin + etoposide

Research question	**Therapeutic indication**[a]	**ACT**[b, c]
1	Extensive Stage Small Cell Lung Cancer (ES-SCLC)	**Carboplatin + etoposide** or cisplatin + etoposide

a. For the present therapeutic indication, the G-BA assumed patients to have stage IV SCLC (staging according to IASLC and UICC). Moreover, the G-BA assumed that prophylactic radiation of the skull was performed and documented in both study arms. Regular monitoring for brain metastases by means of imaging techniques is necessary for patients who received no prophylactic radiation of the skull.
b. It is assumed that platinum-based first-line chemotherapy had been completed by the time maintenance treatment with atezolizumab monotherapy was initiated. According to available evidence, performance of maintenance treatment after initial response to the first-line treatment presents no standard in the treatment of ES-SCLC, because a benefit regarding long-term survival has not been demonstrated to date. Therefore, it is assumed that BSC was available to the patients in the control arm. BSC is understood as the therapy that ensures the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.
c. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

ACT: appropriate comparator therapy; BSC: best supportive care; ES SCLC: Extensive Stage Small Cell Lung Cancer; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; UICC: Union for International Cancer Control

With the combination of carboplatin and etoposide, the company chose one of the options of the ACT specified by the G-BA.

The assessment was made by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. RCTs were used for the derivation of the added benefit. This concurs with the inclusion criterion of the company.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on atezolizumab (status: 6 August 2019)
- bibliographical literature search on atezolizumab (last search on 6 August 2019)
- search in trial registries for studies on atezolizumab (last search on 6 August 2019)

To check the completeness of the study pool:

- search in trial registries for studies on atezolizumab (last search on 17 October 2019)

The check identified no additional relevant study.

2.3.1 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: atezolizumab + carboplatin + etoposide vs. carboplatin + etoposide

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
IMpower133	Yes	Yes	No
a. Study for which the company was sponsor. RCT: randomized controlled trial			

Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
IMpower133	RCT, parallel, double-blind	Adults with untreated[b] ES-SCLC, with ECOG 0 or 1	Global cohort: atezolizumab + carboplatin + etoposide (N = 201) placebo + carboplatin + etoposide (N = 202) cohort in China atezolizumab + carboplatin + etoposide (N = 57) placebo + carboplatin + etoposide (N = 53)	Screening: 28 days treatment: ▪ study medication for 4 cycles (21 days each) ▪ from the 5th cycle: ▫ intervention arm: atezolizumab monotherapy ▫ comparator arm: placebo ▪ in each case, treatment until disease progression, unacceptable intolerance, initiation of another tumour therapy, withdrawal of consent or death; administration of atezolizumab beyond progression was possible at the investigator's discretion if clinical benefit continued to exist. observation: outcome-specific, at most until death, withdrawal of consent or end of the study[c]	Global cohort: 106 centres in Australia, Austria, Brazil, Chile, China, Czech Republic, France, Germany, Greece, Hungary, Italy, Japan, Mexico, Poland, Russia, Serbia, South Korea, Spain, Taiwan, United Kingdom, USA 06/2016–ongoing data cut-offs: 24 April 2018[d] 24 January 2019[e] Cohort in China: 12 centres in China and Taiwan 09/2016–ongoing Data cut-offs: 29 October 2018[f] 24 January 2019[g]	Primary: overall survival, PFS secondary: symptoms, health status, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment. b. Patients who had received chemoradiotherapy for the treatment of a limited SCLC before, had to have received it with curative intent and had to have a treatment-free interval of ≥ 6 months since the last chemotherapy, radiotherapy or chemoradiotherapy cycle. c. The study was scheduled to end after the last visit of the last patient (including the cohort in China), the occurrence of about 306 deaths in the global cohort and enough deaths in the cohort in China. d. Primary analysis of PFS after 360 events (planned after about 295 events); simultaneously planned interim analysis of overall survival after 238 events (planned after about 240 events). e. Analysis of overall survival at the request of EMA within the framework of the approval. Originally planned as a final analysis of overall survival after 306 events; however, since the "stop criterion" pre-specified for the outcome "overall survival" had already been reached at the time point of the interim analysis, the final analysis was considered an exploratory analysis. f. Primary analysis of PFS after 95 events (planned after approx. 90 events). g. First analysis of PFS after 61 events (planned after about 55 events); another analysis of overall survival was planned after 83 events. AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; ES-SCLC: Extensive Stage Small Cell Lung Cancer; N: number of randomized (included) patients; PFS: progression-free survival; RCT: randomized controlled trial; SCLC: small cell lung cancer					

Table 7: Characteristics of the intervention – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide(multipage table)

Study	Intervention	Comparison
IMpower133	Induction phase (4 21-day cycles): atezolizumab 1200 mg IV on day 1 of a cycle + carboplatin, dosage to obtain an area under the concentration-time curve (AUC): 5 mg/mL/min IV on day 1 of a cycle + etoposide 100 mg/m² BSA IV on days 1, 2 and 3 of a cycle maintenance phase: atezolizumab 1200 mg IV on day 1 of a 21-day cycle	Induction phase (4 21-day cycles): placebo IV on day 1 of a cycle + carboplatin, dosage to obtain an AUC: 5 mg/mL/min IV on day 1 of a cycle + etoposide 100 mg/m² BSA IV on days 1, 2 and 3 of a cycle maintenance phase: placebo IV on day 1 of a 21-day cycle
	▪ Treatment was to be continued until disease progression was demonstrated via RECIST 1.1, but could be continued at the investigator's discretion under certain conditions[a]. ▪ Treatment discontinuations due to toxicity were possible. Dose adjustments were only allowed for carboplatin and etoposide.[b] If one component of the study medication was discontinued due to toxicity, treatment with the other components could be continued until progression.	
	Premedication before administration of the study medication: ▪ No premedication was allowed before the administration of the first dose of atezolizumab or placebo. From cycle 2, premedication with antihistamines was possible at the investigator's discretion. ▪ For the administration of carboplatin and etoposide, premedication with antiemetics and IV volumes according to local standards was possible. ▪ The use of corticosteroids should be minimized if clinically possible. **Non-permitted pretreatment:** ▪ systemic therapy with ES-SCLC ▪ systemic immunosuppressive therapy (e.g. corticosteroids) within 1 week before randomization **Permitted concomitant treatment** ▪ continuation of therapies such as hormone replacement therapy, anticoagulation treatment at stable doses ▪ palliative radiotherapy (e.g. for bone metastases), provided they do not restrict the assessment of tumour target lesions; palliative thoracic irradiation ▪ prophylactic irradiation of the skull during the maintenance phase ▪ inhaled corticosteroids at chronic obstructive pulmonary disease, mineralocorticoids and low-dose corticosteroids in patients with orthostatic hypotension or insufficiency of the adrenal cortex **Non-permitted concomitant treatment** ▪ any tumour treatment until disease progression and discontinuation of the study medication ▪ denosumab[c]	

Table 7: Characteristics of the intervention – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide(multipage table)

Study	Intervention	Comparison
a. Treatment could be continued after disease progression if the following criteria were met: clinical benefit from the treatment, no deterioration of the general condition due to disease progression, no disease progression that cannot be treated with permitted concomitant medication (e.g. leptomeningeal disease), patient consent. b. Toxicity-related dose adjustments up to treatment discontinuation were made without relevant deviations from the requirements of the SPC. c. Bisphosphonates were not excluded. Patients who had taken denosumab before the start of the study had to agree to switch to bisphosphonates. AUC: area under the curve, BSA: body surface area; ES-SCLC: Extensive Stage Small Cell Lung Cancer; IV: intravenous; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours		

The included study Impower133 is a double-blind, placebo-controlled RCT. Patients in the intervention group received atezolizumab in combination with carboplatin and etoposide. The control group received placebo in combination with carboplatin and etoposide.

The study included adult patients with ES-SCLC who had not yet received systemic treatment against ES-SCLC. Prior radiochemotherapy was only allowed to be used in a curative treatment approach for limited stage SCLC. The treatment-free interval until diagnosis of the ES-SCLC had to be at least 6 months. Patients with brain metastases could be included if these had been treated and were asymptomatic at the time point of inclusion. Prophylactic irradiation of the skull during the maintenance treatment was allowed. The general condition of the patients had to concur with an ECOG PS of 0 or 1. Therefore, there are no data for patients with untreated or symptomatic brain metastases and for patients with ECOG PS $\geq$ 2.

A total of 403 patients worldwide were randomly assigned to treatment with atezolizumab + carboplatin + etoposide (hereinafter referred to as atezolizumab arm; N = 201) or placebo + carboplatin + etoposide- (hereinafter referred to as placebo arm; N = 202) in a 1:1 ratio. Here, stratification was performed according to ECOG PS (0 vs. 1), sex (male vs. female) and presence of brain metastases (yes vs. no). In addition to this global cohort, there was a cohort in China with the same study protocol, which started later and was investigated separately. This cohort is described in the following section.

Patients in the atezolizumab arm received atezolizumab as an infusion on day 1 of a 3-week cycle for a total of 4 cycles; in the placebo arm, patients received placebo as an infusion, each followed by carboplatin and etoposide on days 1, 2 and 3 of a 3-week cycle. Following the 4th cycle, treatment with atezolizumab or placebo as maintenance therapy was continued and treatment with carboplatin and etoposide was terminated. Application of the drugs largely corresponded to the requirements of the SPC and the guidelines [3-7]. The permitted concomitant treatment in the placebo arm is considered a sufficient implementation of the best supportive care (BSC) during the maintenance phase.

Treatment was performed until disease progression, unacceptable toxicity, start of another tumour therapy, withdrawal of consent or death; administration of atezolizumab could be continued beyond progression at the investigator's discretion if clinical benefit continued to exist.

The study documents contained no restrictions with regard to treatment after the end of the study medication. Follow-up treatments were sufficiently balanced in the study arms (see Table 31 in Appendix E of the full dossier assessment).

Co-primary outcomes of the Impower133 study were "PFS" and "overall survival". Patient-relevant secondary outcomes were outcomes of the categories "morbidity" (symptoms, health status), "health-related quality of life" and "side effects".

The patients underwent outcome-specific observation, maximally until death, withdrawal of consent or end of the study. The study was to be terminated when the following criteria had been met: last visit of the last patient (including cohort in China) and observation of about 306 deaths in the global cohort and a sufficient number of events in overall survival in the cohort in China.

In the IMpower133 study, several data cut-offs were planned, which are described in detail below. Unblinding of the study sponsor was planned after the first data cut-off, which was used as basis for the primary analysis of PFS and an interim analysis of overall survival.

Subpopulation of the IMpower133 study (cohort in China)

According to the company, additional patients from China (N = 100) and Taiwan (N = 10) were recruited for the purpose of an approval in China. Within this framework, 57 patients were treated with atezolizumab + carboplatin + etoposide and 53 patients received the control intervention carboplatin + etoposide. According to the study protocol, recruitment took place after completion of the recruitment phase of the global cohort into a separate cohort. The patients were treated according to the same study protocol and SAP as the global study population, but the data were analysed and presented separately. The company did not use the results of the cohort in China for the derivation of an added benefit, but presented them as supplementary information in a separate section in Module 4 A. As justification, the company cited differences in the baseline characteristics, e.g. ethnic origin, age group distribution, gender distribution, ECOG PS, and smoking status in addition to regulatory reasons.

However, the patients of the cohort in China represent a relevant subpopulation of the IMpower133 study and are included in the present benefit assessment (for reasons, see Section 2.7.4.1 of the full dossier assessment). It should be noted that the separate analyses presented for the two cohorts are not completely disjunct, as 10 patients were included both in the analysis of the global cohort and in the analysis of the cohort in China. The proportion of patients considered twice is only 2% compared to the total study population, so that a meta-analysis is possible. Therefore, a meta-analysis of the results of both cohorts was performed, where

possible. However, in principle it would be appropriate to perform a joint analysis of the individual patient data (IPD) of both cohorts. The company did not present such analyses, however.

Analysis and data cut-offs

In the IMpower133 study, analyses were planned at 2 time points for both the global cohort and the cohort in China.

In the global cohort, the primary analysis of the PFS and an interim analysis of overall survival were carried out after the occurrence of approximately 240 deaths (data cut-off: 24 April 2018). From the point of view of the company, this data cut-off represents the basis for the final analysis, because an effect size pre-specified in the study documents had been achieved. The company used this analysis for the derivation of an added benefit. The results of the second data cut-off (24 January 2019), originally planned as final analysis of overall survival after approx. 306 deaths, were requested by the European Medicines Agency (EMA) within the framework of the approval process and only presented as supplementary information in the present benefit assessment.

For the cohort in China, the first data cut-off (29 October 2018) concurs with the planned primary analysis of PFS (after approx. 90 events). At this point in time, the results on overall survival were assumed to be insufficiently precise. The number of events of approx. 55 deaths required for the planned analysis of overall survival was reached at the second data cut-off (24 January 2019). Another analysis of overall survival was planned to take place after approx. 83 deaths.

Where possible, the results of both cohorts at the respective later data cut-off (24 January 2019) were used for the present benefit assessment.

Further explanations on the several data cut-offs are found in Section 2.7.4.1 of the full dossier assessment.

Treatment duration and follow-up observation

Table 8 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide

Study **Outcome category** **Outcome**	**Planned follow-up observation**
IMpower133	
Mortality	
Overall survival	Until death, discontinuation of study participation or termination of study by the sponsor
Morbidity	
Symptoms (EORTC QLQ-LC13 and EORTC QLQ-C30)	3 and 6 months after progression with discontinuation of the study medication as well as 3 and 6 months after the last study medication for patients who continued treatment after progression.
Health status (EQ-5D VAS)	At each visit for tumour assessment for patients who discontinued the study medication for reasons other than progression
Health-related quality of life (EORTC QLQ-C30)	
Side effects	
SAEs/specific AEs	90 days after administration of the last dose or start of a new systemic therapy
Further AEs	30 days after administration of the last dose or start of a new systemic therapy

AE: adverse event; EORTC: European Organization for Research and Treatment of Cancer; EQ-5D: European Quality of Life5 Dimensions; QLQ-C30: Quality of Life Questionnaire - Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

In the Impower133 study, only the outcome “overall survival” was to be recorded until the end of the study participation.

The outcomes on symptoms, health status and health-related quality of life were recorded beyond the end of treatment. However, the observation periods for these outcomes were systematically shortened, since they were only observed until 6 months after progression. Side effects were only recorded for the period of treatment with the study medication (plus 90 days for SAEs and specific AEs or plus 30 days for further AEs). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, however, it would be necessary to record and analyse these outcomes over the entire period, as was the case for survival.

Characteristics of the study population

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide (multipage table)

Study Characteristics Category	**Atezolizumab + carboplatin + etoposide**	**Placebo + carboplatin + etoposide**
IMpower133	N[a] = 201	N[a] = 202
Age [years], mean (SD)	64 (9)	64 (9)
Sex [F/M], %	36 / 64	35 / 65
Baseline ECOG PS, n (%)		
0	73 (36.3)	67 (33.2)
1	128 (63.7)	135 (66.8)
Family origin, n (%)		
White	163 (81.1)	159 (78.7)
Asian	33 (16.4)	36 (17.8)
Other	5 (2.5)	7 (3.5)
Geographical region, n (%)		
Europe	116 (57.7)	107 (53.0)
America	45 (22.4)	55 (27.2)
Asia-Pacific or Australia	40 (19.9)	40 (19.8)
Smoking status, n (%)		
Never	9 (4.5)	3 (1.5)
Current	74 (36.8)	75 (37.1)
Former	118 (58.7)	124 (61.4)
Brain metastases at baseline, n (%)		
Yes	17 (8.5)	18 (8.9)
No	184 (91.5)	184 (91.1)
Treatment discontinuation, n (%)[b, c]	174 (87.9[d])	186 (94.9[d])
Study discontinuation, n (%)[c, f]	124 (61.7)	142 (70.3)
Impower133 (cohort in China)	N = 57	N = 53
Age [years], mean (SD)	60 (9)	61 (9)
Sex [F/M], %	19 / 81	23 / 77
Baseline ECOG PS, n (%)		
0	7 (12.3)	2 (3.8)
1	50 (87.7)	51 (96.2)
Family origin, n (%)		
Asian	57 (100)	53 (100)
Geographical region, n (%)		
Asia-Pacific or Australia	57 (100)	53 (100)
Smoking status, n (%)		
Never	13 (22.8)	13 (24.5)
Current	9 (15.8)	10 (18.9)
Former	35 (61.4)	30 (56.6)

Table 9: Characteristics of the study population – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide (multipage table)

Study Characteristics Category	Atezolizumab + carboplatin + etoposide	Placebo + carboplatin + etoposide
Brain metastases at baseline, n (%)		
Yes	2 (3.5)	2 (3.8)
No	55 (96.5)	51 (96.2)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)[e, f]	35 (61.4)	34 (64.2)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Data also comprise the reason for discontinuation "death": atezolizumab arm n = 10 vs. placebo arm n = 8.
c. Data cut-off: 24 April 2018.
d. Institute's calculation.
e. Data also comprise the reason for discontinuation "death"; IMpower133: atezolizumab arm n = 101 vs. placebo arm n = 132; IMpower133 (cohort in China): atezolizumab arm n = 31 vs. placebo arm n = 30.
f. Data cut-off: 24 January 2019.

ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics of the two cohorts (global and China) were sufficiently balanced between the treatment arms.

The mean age of the patients in the global cohort included in the IMpower133 study was 64 years; most of them were male. About 80% where white, the proportion of patients with Asian family origin was about 17%. About two thirds had an ECOG PS of 1, the ECOG PS of the other patients was 0. Most of them had no brain metastases.

By definition, the subpopulation of the cohort in China differed primarily by family origin. Whilst the cohort in China only included Asian patients, their proportion in the global cohort was only 17%. Further differences were found in the distribution of age groups, sex, ECOG PS and smoking status. The biggest difference pertained to the smoking status. Whilst one third of the cohort in China were never smokers, the proportion of never smokers in the global cohort was 3%. The proportion of patients with an ECOG PS of 1 was clearly higher in the cohort in China (approx. 90%) than in the global cohort (65%). Table 10 shows the mean/median treatment durations of the patients and the median observation periods for individual outcomes.

Table 10: Information on the study course – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide

Study **Duration of the study phase** **Outcome category**	**Atezolizumab + carboplatin + etoposide**	**Placebo + carboplatin + etoposide**
IMpower133	N[a] = 198	N[a] = 196
Treatment duration [months]		
Median [min; max][b]	4.7 [0; 21]	4.1 [0; 21]
Mean (SD)[b]	5.7 (4.4)	5.0 (3.5)
Observation period [months]		
Overall survival		
Median [min; max][c]	23.1 [0.0; 29.5]	22.6 [0.0; 30.7]
Mean (SD)	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND	ND
IMpower 133 (cohort in China)	N[a] = 57	N[a] = 53
Treatment duration [months]		
Median [min; max][c]	3.7 [0.0; 17.0]	3.7 [1.0; 12.0]
Mean (SD)[c]	5.1 (3.9)	4.2 (2.1)
Observation period [months]		
Overall survival		
Median [min; max][c]	14.3 [0.0; 19.4]	14.0 [0.9; 20.8]
Mean (SD)	N D	N D
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND	ND

a. Number of patients who received at least one dose of the study medication (safety population).
b. Data cut-off: 24 April 2018.
c. Data cut-off: 24 January 2019.

max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

There were neither relevant differences in the treatment duration/observation period between the intervention group and the control group, nor relevant differences in the treatment duration/observation period between the two subpopulations of the included IMpower133 study.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
IMpower133	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

For the IMpower133 study, the risk of bias across outcomes was rated as low. This concurs with the company's assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

- Mortality
  - Overall survival
- Morbidity
  - Symptoms measured with the symptom scales of the instruments European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and Quality of Life Questionnaire Lung Cancer 13 (QLQ-LC13)
  - Health status measured with the visual scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D)
- Health-related quality of life
  - measured with the EORTC QLQ-C30 functional scales
- Side effects
  - SAEs
  - Discontinuation due to AEs
  - severe AEs (CTCAE Grade 3 and 4)
  - Immune-related AEs, SAEs and severe AEs (CTCAE grade 3 and 4)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.7.4.3 of the full dossier assessment).

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of the outcomes – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide

Study	Outcomes											
	Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3–4)	Immune-related AEs	Immune-related SAEs	Immune-related severe AEs (CTCAE grade 3–4)	Further specific AEs
IMpower133	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
IMpower133 – China	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[a]

a. For the cohort in China, there were no analyses on AE at PT and SOC level (see Section 2.7.4.3.2 of the full dossier assessment).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire Lung Cancer 13; RCT: randomized controlled trial; SOC: System Organ Class; SAE: serious adverse event; VAS: visual analogue scale

2.4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide

Study	Study level	Outcomes											
		Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3–4)	Immune-related AEs[a]	Immune-related SAEs[a]	Immune-related severe AEs (CTCAE grade 3–4)[a]	Further specific AEs
IMpower133	L	L	H[a]	H[a]	H[a]	H[a]	H[a]	N[b]	H[a]	H[a]	H[a]	H[a]	H[a]
IMpower133 – China	L	L	H[c]	H[c]	H[c]	H[c]	H[c]	N[b]	H[c]	H[c]	H[c]	H[c]	-[d]

a. Incomplete observations for potentially informative reasons.
b. Despite the low risk of bias, the certainty of results for the outcome "discontinuation due to AEs" was assumed to be restricted (see Section 2.7.4.2 of the full dossier assessment).
c. Incomplete observations for potentially informative reasons (reasons for treatment discontinuation were not reported).
d. For the cohort in China, there were no analyses on AE at PT and SOC level (see Section 2.7.4.3.2 of the full dossier assessment).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The risk of bias for the results on the outcome "overall survival" was rated as low. This concurs with the company's assessment. However, adequate assessment of the outcome "overall survival" is impossible, since the company submitted all analyses only for the global cohort (see Section 2.4.3).

For the outcomes on symptoms and health-related quality of life as well as on SAEs and severe AEs, the risk of bias of the results was rated as high due to incomplete observations for potentially informative reasons. The company rated the risk of bias as low for these outcomes.

The risk of bias of each of the results on the outcome "discontinuation due to AEs" was rated as low. This concurs with the company's assessment, which assessed the risk of bias for this outcome as low. However, the certainty of results was assumed to be restricted for this outcome (see Section 2.7.4.2 of the full dossier assessment).

Moreover, the outcomes "immune-related AEs", "immune-related SAEs" and "immune-related severe AEs" were used for the assessment. For the results on these outcomes, the risk of bias was assessed retrospectively and also rated as high.

2.4.3 Results

Table 14, Table 15, Table 16 and Table 17 summarize the results of atezolizumab in combination with carboplatin and etoposide in comparison with carboplatin and etoposide in patients with ES-SCLC. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. In Appendix A (of the full dossier assessment), the results of the meta-analyses are presented in the form of Forest plots. The Kaplan-Meier curves submitted by the company are found in Appendix B (of the full dossier assessment). Results on common AEs in the global cohort are presented in Appendix D of the full dossier assessment; data for the cohort in China were lacking.

Table 14: Results (mortality, time to event) – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide

Outcome category **outcome** **Study** **(data cut-off)** **Subgroup**	**Atezolizumab + carboplatin + etoposide**		**Placebo + carboplatin + etoposide**		**Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide**
	N	**Median time to event in months [95% CI]** **patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **patients with event n (%)**	**HR [95% CI]; p-value[a]**
Mortality					
Overall survival					
IMpower133 (24 January 2019)	201	12.3 [10.8; 15.8] 142 (70.6)	202	10.3 [9.3; 11.3] 160 (79.2)	0.76 [0.60; 0.95]; 0.015
IMpower133 – China (24 January 2019)	57	11.4 [8.8; 19.4] 31 (54.4)	53	11.9 [10.0; 16.1] 30 (56.6)	1.04 [0.63; 1.73]; 0.865
Total[b]					0.80 [0.65; 0.99]; 0.038
Subgroup analysis for overall survival					
Age					
IMpower133 (24 April 2018)					
< 65 years	111	12.1 [9.7; 19.4] 57 (51.4)	106	11.5 [9.5; 13.5] 61 (57.5)	0.92 [0.64; 1.32]; 0.661[c]
≥ 65 years	90	12.5 [10.6; 16.6] 47 (52.2)	96	9.6 [8.4; 10.7] 73 (76.0)	0.53 [0.36; 0.77]; 0.001[c]
					Interaction p-value = 0.048[d]
IMpower133 – China (24 January 2019)	no subgroup results available				

a. Effect and CI: Cox model, stratified by sex and ECOG PS at baseline (main population) or by sex (cohort in China); p-value: stratified Log-rank test.
b. Meta-analysis with fixed effect; Institute's calculation.
c. Effect and CI: Cox model, unstratified; p-value: unstratified log-rank test.
d. p-value: likelihood ratio test.

CI: confidence interval; n: number of patients with event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

Table 15: Results (morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide (multipage table)

Outcome category **Outcome** **Study** **(data cut-off)**	**Atezolizumab + carboplatin + etoposide**		**Placebo + carboplatin + etoposide**		**Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide**
	N	**Median time to event in months [95% CI] patients with event n (%)**	**N**	**Median time to event in months [95% CI] patients with event n (%)**	**HR [95% CI]; p-value[a]**
Morbidity					
EORTC QLQ-C30 (symptom scales)[c]					
Appetite loss					
IMpower133 (24 April 2018)	201	6.0 [4.7; 8.9] 87 (43.3)	202	7.1 [5.3; 10.2] 85 (42.1)	1.02 [0.75; 1.38]; 0.904
IMpower133 – China (29 October 2018)	57	9.9 [2.4; NC] 22 (38.6)	53	9.4 [2.8; NC] 24 (45.3)	0.92 [0.51; 1.67]; 0.794
Total[b]					1.00 [0.76; 1.31]; 0.990
Diarrhoea					
IMpower133 (24 April 2018)	201	14.1 [8.8; NC] 60 (29.9)	202	10.2 [6.8; NC] 67 (33.2)	0.85 [0.60; 1.21]; 0.362
IMpower133 – China (29 October 2018)	57	NA 10 (17.5)	53	NA 8 (15.1)	1.55 [0.61; 3.95]; 0.353
Total[b]					0.92 [0.66; 1.27]; 0.598
Dyspnoea					
IMpower133 (24 April 2018)	201	12.2 [10.1; NC] 63 (31.3)	202	8.6 [6.3; NC] 72 (35.6)	0.75 [0.53; 1.06]; 0.102
IMpower133 – China (29 October 2018)	57	NA [4.0; NC] 18 (31.6)	53	NA [7.3; NC] 16 (30.2)	1.29 [0.65; 2.57]; 0.463
Total[b]					0.84 [0.61; 1.14]; 0.260
Fatigue					
IMpower133 (24 April 2018)	201	2.8 [1.9; 3.7] 107 (53.2)	202	2.3 [1.8; 3.6] 119 (58.9)	0.88 [0.67; 1.15]; 0.332
IMpower133 – China (29 October 2018)	57	1.9 [0.9; 3.5] 34 (59.6)	53	2.8 [2.1; 6.1] 33 (62.3)	1.24 [0.75; 2.03]; 0.402
Total[b]					0.95 [0.75; 1.21]; 0.681

Table 15: Results (morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide (multipage table)

Outcome category **Outcome** **Study** **(data cut-off)**	**Atezolizumab + carboplatin + etoposide**		**Placebo + carboplatin + etoposide**		**Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide**
	N	**Median time to event in months [95% CI] patients with event n (%)**	**N**	**Median time to event in months [95% CI] patients with event n (%)**	**HR [95% CI]; p-value[a]**
Insomnia					
IMpower133 (24 April 2018)	201	10.4 [6.4; NC] 71 (35.3)	202	9.0 [5.6; NC] 74 (36.6)	0.95 [0.69; 1.32]; 0.772
IMpower133 – China (29 October 2018)	57	11.1 [7.6; NC] 18 (31.6)	53	12.7 [9.4; NC] 19 (35.8)	0.79 [0.41; 1.52]; 0.473
Total[b]					0.92 [0.69; 1.23]; 0.555
Pain					
IMpower133 (24 April 2018)	201	6.0 [4.1; 7.4] 89 (44.3)	202	4.9 [3.5; 7.1] 93 (46.0)	0.90 [0.67; 1.21]; 0.490
IMpower133 – China (29 October 2018)	57	3.8 [2.3; 11.1] 29 (50.9)	53	4.1 [2.3; 12.7] 31 (58.5)	0.96 [0.57; 1.60]; 0.868
Total[b]					0.91 [0.71; 1.18]; 0.494
Nausea and vomiting					
IMpower133 (24 April 2018)	201	3.9 [2.6; 6.6] 98 (48.8)	202	3.5 [2.3; 5.0] 99 (49.0)	0.97 [0.73; 1.28]; 0.814
IMpower133 – China (29 October 2018)	57	10.9 [2.9; NC] 22 (38.6)	53	11.2 [NC] 17 (32.1)	1.25 [0.66; 2.39]; 0.492
Total[b]					1.01 [0.78; 1.31]; 0.939
Constipation					
IMpower133 (24 April 2018)	201	5.3 [3.0; 10.5] 87 (43.3)	202	6.3 [3.0; 9.0] 89 (44.1)	1.00 [0.74; 1.35]; 0.989
IMpower133 – China (29 October 2018)	57	9.9 [4.4; NC] 19 (33.3)	53	NA [9.7; NC] 19 (35.8)	0.97 [0.51; 1.85]; 0.936
Total[b]					0.99 [0.76; 1.31]; 0.969
EORTC QLQ-LC13 (symptom scales)[c]					
Alopecia					
IMpower133 (24 April 2018)	201	0.8 [0.8; 0.8] 154 (76.6)	202	0.8 [0.8; 0.9] 157 (77.7)	1.08 [0.84; 1.37]; 0.563
IMpower133 – China (29 October 2018)	57	0.8 [0.7; 0.9] 42 (73.7)	53	0.7 [0.7; 0.8] 38 (71.7)	1.04 [0.64; 1.69]; 0.873
Total[b]					1.07 [0.86; 1.33]; 0.534

Table 15: Results (morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide (multipage table)

Outcome category **Outcome** **Study** **(data cut-off)**	**Atezolizumab + carboplatin + etoposide**		**Placebo + carboplatin + etoposide**		**Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide**
	N	**Median time to event in months [95% CI] patients with event n (%)**	**N**	**Median time to event in months [95% CI] patients with event n (%)**	**HR [95% CI]; p-value[a]**
Haemoptysis					
IMpower133 (24 April 2018)	201	NA 22 (10.9)	202	NA 25 (12.4)	0.81 [0.46; 1.44]; 0.473
IMpower133 – China (29 October 2018)	57	NA 3 (5.3)	53	NA 8 (15.1)	0.42 [0.11; 1.60]; 0.192
Total[b]					0.73 [0.43; 1.24]; 0.244
Dysphagia					
IMpower133 (24 April 2018)	201	NA [10.6; NC] 49 (24.4)	202	16.6 [8.4; NC] 61 (30.2)	0.73 [0.50; 1.07]; 0.105
IMpower133 – China (29 October 2018)	57	12.3 [12.3; NC] 11 (19.3)	53	9.7 [8.8; NC] 13 (24.5)	0.84 [0.37; 1.90]; 0.677
Total[b]					0.75 [0.53; 1.06]; 0.100
Dyspnoea					
IMpower133 (24 April 2018)	201	4.4 [2.8; 7.6] 90 (44.8)	202	2.8 [2.2; 5.6] 103 (51.0)	0.85 [0.64; 1.14]; 0.270
IMpower133 – China (29 October 2018)	57	2.3 [1.5; 3.5] 33 (57.9)	53	2.9 [1.8; NC] 30 (56.6)	1.34 [0.81; 2.22]; 0.259
Total[b]					0.95 [0.74; 1.22]; 0.695
Coughing					
IMpower133 (24 April 2018)	201	NA [11.6; NC] 53 (26.4)	202	11.6 [6.7; 16.6] 65 (32.2)	0.76 [0.53; 1.10]; 0.142
IMpower133 – China (29 October 2018)	57	NA [4.0; NC] 19 (33.3)	53	7.3 [4.3; NC] 24 (45.3)	0.88 [0.48; 1.62]; 0.682
Total[b]					0.79 [0.58; 1.08]; 0.140
Sore mouth					
IMpower133 (24 April 2018)	201	14.1 [10.0; NC] 63 (31.3)	202	10.6 [5.1; NC] 71 (35.1)	0.80 [0.57; 1.13]; 0.214
IMpower133 – China (29 October 2018)	57	NA 10 (17.5)	53	NA 13 (24.5)	0.85 [0.37; 1.95]; 0.707
Total[b]					0.81 [0.59; 1.11]; 0.184

Table 15: Results (morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide (multipage table)

Outcome category **Outcome** **Study** **(data cut-off)**	**Atezolizumab + carboplatin + etoposide**		**Placebo + carboplatin + etoposide**		**Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide**
	N	**Median time to event in months [95% CI] patients with event n (%)**	**N**	**Median time to event in months [95% CI] patients with event n (%)**	**HR [95% CI]; p-value[a]**
Peripheral neuropathy					
IMpower133 (24 April 2018)	201	5.1 [3.6; 7.9] 87 (43.3)	202	7.0 [5.1; 9.0] 79 (39.1)	1.10 [0.81; 1.50]; 0.540
IMpower133 – China (29 October 2018)	57	NA [5.8; NC] 17 (29.8)	53	8.7 [5.1; 12.7] 22 (41.5)	0.86 [0.45; 1.65]; 0.654
Total[b]					1.05 [0.80; 1.39]; 0.724
Pain (arm/shoulder)					
IMpower133 (24 April 2018)	201	6.9 [5.1; 10.4] 78 (38.8)	202	6.2 [4.2; 10.6] 80 (39.6)	0.93 [0.68; 1.28]; 0.671
IMpower133 – China (29 October 2018)	57	NA [4.6; NC] 19 (33.3)	53	9.7 [7.1; NC] 20 (37.7)	0.96 [0.50; 1.83]; 0.898
Total[b]					0.94 [0.70; 1.24]; 0.647
Pain (chest)					
IMpower133 (24 April 2018)	201	10.9 [6.0; NC] 66 (32.8)	202	11.6 [6.1; NC] 65 (32.2)	0.99 [0.70; 1.40]; 0.958
IMpower133 – China (29 October 2018)	57	11.1 [3.8; NC] 18 (31.6)	53	7.1 [2.3; NC] 25 (47.2)	0.64 [0.35; 1.19]; 0.157
Total[b]					0.89 [0.66; 1.20]; 0.451
Pain (other)					
IMpower133 (24 April 2018)	201	6.5 [3.9; 8.1] 84 (41.8)	202	6.2 [4.4; 10.4] 79 (39.1)	1.04 [0.77; 1.42]; 0.789
IMpower133 – China (29 October 2018)	57	3.8 [2.3; NC] 27 (47.4)	53	7.2 [4.1; 12.7] 26 (49.1)	1.38 [0.79; 2.39]; 0.254
Total[b]					1.11 [0.85; 1.45]; 0.440

Table 15: Results (morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide (multipage table)

Outcome category **Outcome** **Study** **(data cut-off)**	**Atezolizumab + carboplatin + etoposide**		**Placebo + carboplatin + etoposide**		**Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide**
	N	**Median time to event in months [95% CI] patients with event n (%)**	**N**	**Median time to event in months [95% CI] patients with event n (%)**	**HR [95% CI]; p-value[a]**
Health-related quality of life					
EORTC QLQ-C30 (functional scales)[d]					
Global health status					
IMpower133 (24 April 2018)	201	6.5 [4.5; 10.4] 88 (43.8)	202	7.6 [4.2; 9.6] 81 (40.1)	1.01 [0.74; 1.37]; 0.971
IMpower133 – China (29 October 2018)	57	3.8 [2.1; 7.7] 32 (56.1)	53	9.4 [5.7; NC] 22 (41.5)	1.87 [1.07; 3.25]; 0.025
Total[b]					1.17 [0.89; 1.53]; 0.260
Emotional functioning					
IMpower133 (24 April 2018)	201	NA [7.1; NC] 66 (32.8)	202	8.8 [7.6; NC] 74 (36.6)	0.85 [0.61; 1.19]; 0.344
IMpower133 – China (29 October 2018)	57	9.9 [3.0; NC] 23 (40.4)	53	4.2 [2.7; 12.7] 27 (50.9)	0.87 [0.49; 1.55]; 0.632
Total[b]					0.85 [0.64; 1.14]; 0.288
Cognitive functioning					
IMpower133 (24 April 2018)	201	4.2 [2.8; 6.0] 99 (49.3)	202	4.4 [3.0; 7.0] 96 (47.5)	1.00 [0.75; 1.34]; 0.979
IMpower133 – China (29 October 2018)	57	3.8 [2.8; 9.9] 28 (49.1)	53	3.6 [1.4; 7.3] 31 (58.5)	0.81 [0.48; 1.38]; 0.442
Total[b]					0.95 [0.74; 1.23]; 0.706
Physical functioning					
IMpower133 (24 April 2018)	201	5.4 [3.5; 7.2] 98 (48.8)	202	6.2 [3.5; 8.7] 89 (44.1)	1.10 [0.82; 1.47]; 0.540
IMpower133 – China (29 October 2018)	57	3.8 [2.9; 9.9] 30 (52.6)	53	8.3 [3.1; NC] 24 (45.3)	1.38 [0.80; 2.38]; 0.239
Total[b]					1.16 [0.89; 1.50]; 0.267

Table 15: Results (morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide (multipage table)

Outcome category **Outcome** **Study** **(data cut-off)**	**Atezolizumab + carboplatin + etoposide**		**Placebo + carboplatin + etoposide**		**Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide**
	N	**Median time to event in months [95% CI] patients with event n (%)**	**N**	**Median time to event in months [95% CI] patients with event n (%)**	**HR [95% CI]; p-value[a]**
Role functioning					
IMpower133 (24 April 2018)	201	3.7 [3.0; 5.3] 103 (51.2)	202	3.7 [2.6; 5.6] 98 (48.5)	1.04 [0.79; 1.38]; 0.774
IMpower133 – China (29 October 2018)	57	3.8 [2.3; 9.9] 30 (52.6)	53	7.0 [3.1; NC] 25 (47.2)	1.30 [0.76; 2.23]; 0.335
Total[b]					1.09 [0.85; 1.40]; 0.494
Social functioning					
IMpower133 (24 April 2018)	201	7.0 [3.9; 15.6] 83 (41.3)	202	2.8 [2.1; 5.6] 99 (49.0)	0.73 [0.54; 0.98]; 0.038
IMpower133 – China (29 October 2018)	57	4.0 [1.5; NC] 29 (50.9)	53	2.3 [2.1; NC] 29 (54.7)	0.97 [0.57; 1.68]; 0.925
Total[b]					0.78 [0.60; 1.01]; 0.062
Side effects					
AEs (supplementary information)					
IMpower133 (24 April 2018)	198	ND 198 (100)	196	ND 189 (96.4)	–
IMpower133 – China (24 January 2019)	57	ND 57 (100)	52	ND 52 (100)	–
SAEs					
IMpower133 (24 April 2018)	198	ND 74 (37.4)	196	ND 68 (34.7)	1.12 [0.81; 1.56]; 0.494
IMpower133 – China (24 January 2019)	57	ND 21 (36.8)	52	ND 14 (26.9)	1.37 [0.69; 2.70]; 0.366
Total[b]					1.16 [0.87; 1.56]; 0.316
Severe AEs (CTCAE grade 3 or 4)					
IMpower133 (24 April 2018)	198	ND 136 (68.7)[e]	196	ND 136 (69.4)[e]	1.07 [0.84; 1.37]; 0.570
IMpower133 – China (24 January 2019)	57	ND 44 (77.2)[f]	52	ND 43 (82.7)[f]	1.00 [0.65; 1.54]; 0.987
Total[b]					1.05 [0.85; 1.30]; 0.637

Table 15: Results (morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide (multipage table)

Outcome category **Outcome** **Study** **(data cut-off)**	**Atezolizumab + carboplatin + etoposide**		**Placebo + carboplatin + etoposide**		**Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide**
	N	**Median time to event in months [95% CI] patients with event n (%)**	**N**	**Median time to event in months [95% CI] patients with event n (%)**	**HR [95% CI]; p-value[a]**
Discontinuation due to AEs[g]					
IMpower133 (24 April 2018)	198	ND 22 (11.1)	196	ND 6 (3.1)	3.42 [1.38; 8.48]; 0.005
IMpower133 – China (24 January 2019)	57	ND 7 (12.3)	52	ND 0 (0)	NC[h]; 0.010
Total[b]					NC

a. Effect and CI: Cox model, stratified by sex and ECOG PS at baseline (main population) or by sex (cohort in China); p-value: stratified Log-rank test. Outcomes on side effects: effect and CI based on unstratified Cox model; p-value: unstratified log-rank test.
b. Meta-analysis with fixed effect; Institute's calculation.
c. Time to first deterioration; defined as an increase of the score by ≥ 10 points compared with baseline.
d. Time to first deterioration; defined as decrease of the score by ≥ 10 points compared to baseline.
e. Discrepancy between information in Module 4 and Module 5 of the dossier. The data presented come from Module 4. These data were used because no HRs were reported in the study report. In the study report, 133 (67.2%) patients were reported in the atezolizumab arm and 125 (63.8%) in the placebo arm.
f. Discrepancy between information in Module 4 and Module 5 of the dossier. The data presented come from Module 4. These data were used because no HRs were reported in the study report. In the study report, 42 (73.7%) patients were reported in the atezolizumab arm and 42 (80.8 %) in the placebo arm.
g. Discontinuation of at least one treatment component.
h. The HR could not be estimated, since no events occurred in the placebo arm.

AE: adverse event; CI: confidence interval; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; NC: not calculable; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 16: Results (side effects, dichotomous) – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide

Outcome category **Outcome** **Study (data cut-off)**	**Atezolizumab + carboplatin + etoposide**		**Placebo + carboplatin + etoposide**		**Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
Side effects					
Immune-related AEs					
IMpower133 (24 April 2018)	198	79 (39.9)	196	48 (24.5)	ND
IMpower133 – China (24 January 2019)	57	31 (54.4)	52	20 (38.5)	ND
Total					1.57 [1.23; 2.01]; < 0.001
Immune-related SAEs					
IMpower133 (24 April 2018)	198	13 (6.6)	196	7 (3.6)	ND
IMpower133 – China (24 January 2019)	57	4 (7.0)	52	0 (0)	ND
Total					2.36 [0.997; 5.60]; 0.044[b]
Immune-related AEs with CTCAE grade 3 and 4					
IMpower133 (24 April 2018)	198	16 (8.1)	196	5 (2.6)	ND
IMpower133 – China (24 January 2019)	57	4 (7.0)	52	4 (7.7)	ND
Total					2.16 [1.004; 4.65]; 0.043

a. Institute‘s calculation of effect RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [8]).
b. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 17: Results (morbidity, continuous) – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide

Outcome category Outcome Study (data cut-off)	Atezolizumab + carboplatin + etoposide			Placebo + carboplatin + etoposide			Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide
	N[a]	Values at baseline mean (SD)	Values at week 12 mean (SD)	N[a]	Values at baseline mean (SD)	Values at week 12 mean (SD)	MD [95% CI]; p-value[b]
Morbidity							
Health status (EQ-5D VAS)[c]							
IMpower133 (24 April 2018)	132	63.43 (19.46)	69.80 (18.87)	146	65.10 (20.55)	72.10 (18.28)	−2.30 [−6.68; 2.08] ND
IMpower133 – China (29 October 2018)	38	77.86 (13.45)	78.24 (11.72)	42	77.49 (16.76)	78.10 (14.24)	0.14 [−5.55; 5.83] ND
Total[d]							−1.39 [−4.86; 2.08]; 0.431

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b. Institute's calculation based on mean and standard deviation at week 12.
c. Higher values mean better health-related quality of life; positive effects mean an advantage for intervention.
d. Meta-analysis with fixed effect; Institute's calculation.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Due to the high risk of bias at outcome level, no more than hints, e.g. of an added benefit, can be determined for the outcomes "morbidity", "health-related quality of life" and "side effects". A hint can be determined for the outcome "overall survival". The company derived the added benefit on the basis of the global cohort of the Impower133 study alone. However, the cohort in China was also considered relevant for the present benefit assessment. Therefore, a meta-analysis of the two cohorts was performed, where possible.

Mortality

For the outcome "overall survival", the meta-analysis of the results of both cohorts of Impower133 showed a statistically significant difference in favour of atezolizumab + carboplatin + etoposide. Thereby, the CI_u was 0.99 and thus very close to the zero effect.

In addition, the global cohort shows an effect modification by the characteristic age. The p-value of the interaction test is only slightly below the significance level of 0.05 (p = 0.048). With regard to the individual subgroups, a statistically significant difference in favour of atezolizumab + carboplatin + etoposide with the extent "considerable" only results for patients

aged 65 years and older. For patients in the age group < 65 years, in contrast, there is no statistically significant difference between the treatment groups.

Since subgroup analyses are neither available for the cohort in China nor for both cohorts together, it is unclear how the addition of the cohort in China affects the effect modification. Basically, the assessment of effect modification by the characteristic "age" can change through the addition of the data of the cohort in China due to the very narrow results of the interaction test. Thus, an adequate assessment of the added benefit for the outcome "overall survival" cannot be made without the corresponding subgroup analyses of the cohort in China or, at the meta-level, the results of both cohorts.

This deviates from the assessment of the company, which considered the effect modification not to be relevant and derived an indication of an added benefit of atezolizumab for the total population.

Morbidity

Symptoms

Symptom outcomes were recorded with the symptom scales of the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-LC13. The time to deterioration by at least 10 points was considered. There are no statistically significant group differences for any of the outcomes on symptoms. This resulted in no hint of an added benefit of atezolizumab in combination with carboplatin and etoposide in comparison with carboplatin and etoposide for any of the outcomes on symptoms. An added benefit is therefore not proven.

Health status

At week 12, there was no statistically significant difference between the treatment arms for the outcome "health status" measured using the EQ-5D VAS. This resulted in no hint of an added benefit of atezolizumab in combination with carboplatin and etoposide in comparison with carboplatin and etoposide. An added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded with the functional scales and with the scale for recording the global health status of the disease-specific instrument EORTC QLQ-C30. The time to deterioration by at least 10 points was considered. There was no statistically significant difference between the treatment groups for any of the scales mentioned above.

In the global cohort, there is an effect modification by the characteristic "smoking status" for the outcome "cognitive functioning". However, since no subgroup analyses were available for the cohort in China, the results were not conclusively interpretable. A detailed reason can be found in Section 2.4.4.

Thus, there is no hint of an added benefit for the outcomes on "health-related quality of life". An added benefit is therefore not proven for these outcomes.

Side effects

SAEs, severe AEs (CTCAE grade 3 and 4)

No statistically significant difference between the treatment groups was shown for the outcomes "SAEs" and "severe AEs (CTCAE grade 3 or 4)". This resulted in no hint of greater or lesser harm from atezolizumab in combination with carboplatin + etoposide in comparison with carboplatin and etoposide for the outcomes "SAEs" and "severe AEs (CTCAE grade 3 and 4)". Greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference between the treatment groups to the disadvantage of atezolizumab in combination with carboplatin and etoposide was shown for the outcome "discontinuation due to AEs". This resulted in no hint of greater harm from atezolizumab in combination with carboplatin and etoposide in comparison with carboplatin + etoposide for this outcome.

Specific AEs

Immune-related AEs, immune-related SAEs, immune-related severe AEs (CTCAE grade 3 and 4)

A statistically significant difference between the treatment groups to the disadvantage of atezolizumab in combination with carboplatin and etoposide was shown for each of the outcomes "immune-related AEs", "immune-related SAEs" and "immune-related severe AEs". This resulted in a hint of greater harm from atezolizumab in combination with carboplatin and etoposide in comparison with carboplatin and etoposide for each of these outcomes.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present assessment:

- sex (female versus male)
- age (< 65 years versus ≥ 65 years)
- Family origin (white vs. Asian vs. other)
- Smoking status (never vs. current vs. former)
- brain metastases (yes versus no)

Of these selected subgroup characteristics, only analyses on age and sex were available for all outcomes on side effects. Since subgroup analyses were only available for the global cohort, but not for the cohort in China, the subgroup analyses presented were not used to derive the added benefit and are only presented as supplementary information for the global cohort. Interaction tests were performed if at least 10 patients per subgroup were included in the analysis. For binary data, 10 events had to have occurred in at least 1 subgroup.

Only results involving an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) were presented. Moreover, subgroup

results were only presented if there was a statistically significant and relevant effect in at least one subgroup.

Table 18 summarizes the subgroup results of atezolizumab + carboplatin + etoposide in comparison with carboplatin + etoposide provided as supplementary information.

Table 18: Subgroups (mortality morbidity, health-related quality of life) – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide (multipage table)

Study Outcome Characteristic Subgroup	Atezolizumab + carboplatin + etoposide		Placebo + carboplatin + etoposide		Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide	
	N	Median time to event in months [95 % CI] Patients with event n (%)	N	Median time to event in months [95 % CI] Patients with event n (%)	HR [95% CI][a]	p-value[b]
IMpower133						
Health-related quality of life						
EORTC QLQ-C30 - cognitive functioning[c]						
Smoking status						
Never	9	0.8 [0.7; 3.3] 5 (55.6)	3	NA [3.6; NC] 1 (33.3)	–[d]	0.012
Current	74	3.8 [2.1; 7.9] 38 (51.4)	75	5.1 [2.9; 8.8] 33 (44.0)	1.06 [0.66; 1.69]	0.823
Former	118	5.3 [3.3; 7.0] 56 (47.5)	124	4.1 [2.3; 7.6] 62 (50.0)	0.90 [0.62; 1.29]	0.559
Total					Interaction:	0.046

a. Unstratified Cox regression model
b. p-value for the effect estimate from log-rank test, interaction test: likelihood ratio test.
c. Time to first deterioration; defined as decrease of the score by ≥ 10 points compared with baseline.
d. No presentation of effect estimation and CI as these are not informative.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial

Health-related quality of life

Cognitive functioning

In the global cohort, there is an effect modification by the characteristic “smoking status” for the outcome “cognitive functioning”.

In the subgroup of never smokers, there is a statistically significant difference in “cognitive functioning” to the disadvantage of atezolizumab in combination with carboplatin and etoposide in comparison with carboplatin and etoposide. In the subgroup of former smokers

and in the subgroup of active smokers, however, there was no statistically significant difference between the treatment groups.

Since no subgroup analyses are available for the cohort in China, and the proportion of never smokers is higher than in the global cohort (24% vs. 3%), it is unclear how the addition of the cohort in China affects the effect modification. Basically, the assessment of effect modification by the characteristic "smoking status" can change through the addition of the data of the cohort in China due to the very narrow results of the interaction test. Thus, this effect modification cannot be conclusively interpreted without the corresponding subgroup analyses for the cohort in China.

This deviates from the assessment of the company in so far as the company considered the effect modification not to be relevant and consequently derived no hint of an added benefit of atezolizumab in combination with carboplatin and etoposide for the total population for this outcome on the basis of the global cohort.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 19).

Determination of the outcome category for the outcomes on "symptoms"

The dossier does not state for every outcome considered in the present benefit assessment whether it was non-serious/non-severe or serious/severe. The classification of these outcomes is justified below.

Discontinuation due to AEs

The proportion of discontinuations due to a severe AE or SAE is not known for the outcome "discontinuation due to AEs". The outcome was therefore allocated to the category "non-serious/non-severe side effects".

The subsequent Table 19 describes the extent of added benefit at outcome level, based on the data of the Impower133 study presented in Section 2.4.3.

Table 19: Extent of added benefit at outcome level: atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide (multipage table)

Outcome category **Outcome**	**Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide** **Median time to event** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	No usable analyses	Lesser benefit/added benefit not proven
Morbidity		
Symptoms		
EORTC QLQ-C30 (symptom scales) – time to deterioration[c]		
Appetite loss	Median: 6.0 and 9.9 vs. 7.1 and 9.4 HR: 1.00 [0.76; 1.31] p = 0.990	Lesser benefit/added benefit not proven
Diarrhoea	Median: 14.1 and NA vs. 10.2 and NA HR: 0.92 [0.66; 1.27] p = 0.598	Lesser benefit/added benefit not proven
Dyspnoea	Median: 12.2 and NA vs. 8.6 and NA HR: 0.84 [0.61; 1.14] p = 0.260	Lesser benefit/added benefit not proven
Fatigue	Median: 2.8 and 1.9 vs. 2.3 and 2.8 HR: 0.95 [0.75; 1.21] p = 0.681	Lesser benefit/added benefit not proven
Insomnia	Median: 10.4 and 11.1 vs. 9.0 and 12.7 HR: 0.92 [0.69; 1.23] p = 0.555	Lesser benefit/added benefit not proven
Pain	Median: 6.0 and 3.8 vs. 4.9 and 4.1 HR: 0.91 [0.71; 1.18] p = 0.494	Lesser benefit/added benefit not proven
Nausea and vomiting	Median: 3.9 and 10.9 vs. 3.5 and 11.2 HR: 1.01 [0.78; 1.31] p = 0.939	Lesser benefit/added benefit not proven
Constipation	Median: 5.3 and 9.9 vs. 6.3 and NA HR: 0.99 [0.76; 1.31] p = 0.969	Lesser benefit/added benefit not proven

Table 19: Extent of added benefit at outcome level: atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide (multipage table)

Outcome category **Outcome**	**Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide** **Median time to event** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
EORTC QLQ-LC13 (symptom scales) – time to deterioration[c]		
Alopecia	Median: 0.8 and 0.8 vs. 0.8 and 0.7 HR: 1.07 [0.86; 1.33] p = 0.534	Lesser benefit/added benefit not proven
Haemoptysis	Median: NA and NA vs. NA and NA HR: 0.73 [0.43; 1.24] p = 0.244	Lesser benefit/added benefit not proven
Dysphagia	Median: NA und 12.3 vs. 16.6 and 9.7 HR: 0.75 [0.53; 1.06] p = 0.100	Lesser benefit/added benefit not proven
Dyspnoea	Median: 4.4 and 2.3 vs. 2.8 and 2.9 HR: 0.95 [0.74; 1.22] p = 0.695	Lesser benefit/added benefit not proven
Cough	Median: NA and NA vs.11.6 and 7.3 HR: 0.79 [0.58; 1.08] p = 0.140	Lesser benefit/added benefit not proven
Sore mouth	Median: 14.1 and NA vs. 10.6 and NA HR: 0.81 [0.59; 1.11] p = 0.184	Lesser benefit/added benefit not proven
Peripheral neuropathy	Median: 5.1 and NA vs. 7.0 and 8.7 HR: 1.05 [0.80; 1.39] p = 0.724	Lesser benefit/added benefit not proven
Pain (arm/shoulder)	Median: 6.9 and NA vs. 6.2 and 9.7 HR: 0.94 [0.70; 1.24] p = 0.647	Lesser benefit/added benefit not proven
Pain (chest)	Median: 10.9 and 11.1 vs. 11.6 and 7.1 HR: 0.89 [0.66; 1.20] p = 0.451	Lesser benefit/added benefit not proven
Pain (other)	Median: 6.5 and 3.8 vs. 6.2 and 7.2 HR: 1.11 [0.85; 1.45] p = 0.440	Lesser benefit/added benefit not proven
Health status		
(EQ-5D VAS)	Mean (week 12): 69.8 and 78.2 vs. 72.1 and 78.1[d] MD: −1.39 [−4.86; 2.08] p = 0.431	Lesser benefit/added benefit not proven

Table 19: Extent of added benefit at outcome level: atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide (multipage table)

Outcome category **Outcome**	**Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide** **Median time to event** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
EORTC QLQ-C30 (functional scales) – time to deterioration[c]		
Global health status	Median: 6.5 and 3.8 vs. 7.6 and 9.4 HR: 1.17 [0.89; 1.53] p = 0.260	Lesser benefit/added benefit not proven
Emotional functioning	Median: NA und 9.9 vs. 8.8 and 4.2 HR: 0.85 [0.64; 1.14] p = 0.288	Lesser benefit/added benefit not proven
Cognitive functioning	No usable analyses	Lesser benefit/added benefit not proven
Physical functioning	Median: 5.4 and 3.8 vs. 6.2 and 8.3 HR: 1.16 [0.89; 1.50] p = 0.267	Lesser benefit/added benefit not proven
Role functioning	Median: 3.7 and 3.8 vs. 3.7 and 7.0 HR: 1.09 [0.85; 1.40] p = 0.494	Lesser benefit/added benefit not proven
Social functioning	Median: 7.0 and 4.0 vs. 2.8 and 2.3 HR: 0.78 [0.60; 1.01] p = 0.062	Lesser benefit/added benefit not proven
Side effects		
SAEs	Median: ND vs. ND HR: 1.16 [0.87; 1.56] p = 0.316	Greater/lesser harm not proven
Severe AEs (CTCAE grade 3–4)	Median: ND vs. ND HR: 1.05 [0.85; 1.30] p = 0.637	Greater/lesser harm not proven
Discontinuation due to AEs	Global cohort Median: ND vs. ND HR: 3.42 [1.38; 8.48]; HR: 0.29 [0.12; 0.72][e]; p = 0.005	Outcome category: “non-serious/non-severe side effects” $CI_u < 0.80$ greater harm, extent: “considerable”[f]
	Cohort in China Median: ND vs. ND HR: NC p = 0.010	
	Probability: “hint”	

Table 19: Extent of added benefit at outcome level: atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide (multipage table)

Outcome category **Outcome**	**Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide** **Median time to event** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Specific AEs		
Immune-related AEs	Proportion of events: 43.1% vs. 27.4% RR: 1.57 [1.23; 2.01] RR: 0.64 [0.50; 0.81][e] p = < 0.001 Probability: "hint"	Outcome category: "non-serious/non-severe side effects" $0.80 \leq CI_u < 0.90$ greater harm, extent: "minor"
Immune-related SAEs	Proportion of events: 6.7% vs. 2.8% RR: 2.36 [0.997; 5.60]; p = 0.044 RR: 0.42 [0.18; 1.003][e] probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "minor"[g]
Immune-related severe AEs (CTCAE grade 3–4)	Proportion of events: 7.8% vs. 3.6% RR: 2.16 [1.004; 4.65]; p = 0.043 RR: 0.46 [0.22; 0.996][e] probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Time to first deterioration; defined as an increase of the score by ≥ 10 points compared with baseline.
d. Minimum and maximum mean per treatment arm in both cohorts.
e. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
f. Derivation is based on qualitative consideration: The effect estimate pertaining to the global cohort points to greater harm with the extent "considerable". The proportion of events of the cohort in China (atezolizumab arm 12.3% vs. placebo arm 0%) support this effect.
g. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods. The assessment of the extent is based on the p-value.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MD: mean difference; NA: not achieved; NC: not calculable; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 20 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 20: Positive and negative effects from the assessment of atezolizumab + carboplatin + etoposide in comparison with placebo + carboplatin + etoposide

Positive effects	**Negative effects**
–	Non-serious/non-severe side effects ▪ discontinuation due to AEs; hint of greater harm – extent "considerable" ▪ immune-related AEs; hint of greater harm - extent: "minor"
–	Serious/severe side effects ▪ immune-related severe AEs (CTCAE grade 3 and 4); hint of greater harm – extent: "minor" ▪ immune-related SAEs; hint of greater harm – extent: "non-quantifiable"
For the outcome "overall survival", there are no usable evaluations for the entire population of the IMpower133 study (global cohort + cohort in China).	
AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events; SAE: serious adverse event	

Based on the available analyses, the overall consideration shows negative effects for the outcomes "discontinuation due to AEs", "immune-related AEs", "immune-related severe AEs" and "immune-related SAEs".

An adequate conclusion on the added benefit cannot be made since usable analyses on overall survival are not available for the total population of IMpower133 (global cohort + cohort in China).

In summary, an added benefit of atezolizumab in combination with carboplatin and etoposide in comparison with carboplatin and etoposide has not been proven for adult patients with ES-SCLC.

Table 21 summarizes the result of the assessment of the added benefit of atezolizumab in combination with carboplatin and etoposide in comparison with the ACT.

Table 21: Atezolizumab in combination with carboplatin and etoposide – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Extensive Stage Small Cell Lung Cancer	**Etoposide + carboplatin** or etoposide + cisplatin	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. The IMpower133 study only included patients with an ECOG PS of 0 or 1 and with treated and asymptomatic brain metastases. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or with untreated or symptomatic brain metastases. ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit for adults with ES-SCLC. The company derived this added benefit on the basis of the global cohort of the IMpower133 study without considering the effect modification by the characteristic "age" for the outcome "overall survival", while for the present benefit assessment the total population of the study including the cohort in China was used as far as data were available (see Section 2.4.3).

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.6 List of included studies

IMpower133

Chugai Pharmaceutical. A phase III, randomized, double-blind, placebo-controlled study of carboplatin plus etoposide with or without atezolizumab (anti-PD-l1 antibody) in patients with untreated extensive-stage small cell lung cancer [online]. In: JAPIC Clinical Trials Information. 10.09.2019 [Accessed: 28.10.2019]. URL: https://www.clinicaltrials.jp/cti-user/trial/ShowDirect.jsp?japicId=JapicCTI-163303.

F. Hoffman-La Roche. A phase I/III, randomized, double-blind, placebo-controlled study of carboplatin plus etoposide with or without atezolizumab (antipd-l1 antibody) in patients with untreated extensive-stage small cell lung cancer [online]. In: EU Clinical Trials Register. [Accessed: 28.10.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-004861-97.

Hoffmann-La Roche. A study of carboplatin plus etoposide with or without atezolizumab in participants with untreated extensive-stage (ES) small cell lung cancer (SCLC) (IMpower133): study details [online]. In: ClinicalTrials.gov. 18.09.2019 [Accessed: 28.10.2019]. URL: https://ClinicalTrials.gov/show/NCT02763579.

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Roche Pharma. A phase I/III, randomized, double-blind, placebo-controlled study of carboplatin plus etoposide with or without atezolizumab (anti-PD-L1 antibody) in patients with untreated extensive-stage small cell lung cancer; study GO30081; Zusatzanalysen [unpublished]. 2018.

Roche Pharma. A phase I/III, randomized, double-blind, placebo-controlled study of carboplatin plus etoposide with or without atezolizumab (anti-PD-L1 antibody) in patients with untreated extensive-stage small cell lung cancer; study GO30081; clinical study report [unpublished]. 2018.

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Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-86-atezolizumab-small-cell-lung-cancer-benefit-assessment-according-to-35a-social-code-book-v.12637.html.