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Atezolizumab (small cell lung cancer) –

Addendum to Commission A19-86[1]

Addendum

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Cornelia Rüdig
- Katharina Hirsch
- Volker Vervölgyi

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Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	Adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
ES-SCLC	Extensive Stage Small Cell Lung Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	Hazard ratio
IPD	individual patient data
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 25 February 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-86 (Atezolizumab – Benefit assessment according to §35a Social Code Book [SGB] V) [1].

In its dossier, the company presented results of the Impower130 study [2] for the assessment of the added benefit of atezolizumab in combination with carboplatin and etoposide in comparison with the appropriate comparator therapy (ACT) for Extensive Stage Small Cell Lung Cancer (ES-SCLC). In addition to a global cohort, the study also included a smaller cohort in China, which started later. Both cohorts were treated according to the same study protocol and statistical analysis plan (SAP), however, the data of the cohort in China were analysed separately. In its dossier, the company did not use the results of the cohort in China for the derivation of an added benefit, but presented the results as supplementary information. Deviating from the company, dossier assessment A19-86 considered the cohort in China relevant and conducted meta-analyses of the two cohorts. However, the results of the cohort in China were incomplete. For instance, subgroup analyses were missing. With its comments [3], the company has now presented meta-analyses of the two cohorts of IMpower133 including subgroup analyses. Moreover, the company presented data on subsequent therapies in the cohort in China as well as information on treatment discontinuations due to adverse events (AEs) in the global cohort.

The G-BA commissioned IQWiG to assess the meta-analysis of the global cohort and the cohort in China presented by the company in the comments as well as the presented comparative data on subsequent therapies in these two cohorts and the information presented on treatment discontinuations due to AEs.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Assessment of the presented comparative data on subsequent therapies

In its argumentation in the comments on why the global cohort and the Chinese cohort of the IMpower133 study should not be considered jointly, the company also mentioned differences in the type of the subsequent therapies between the two cohorts. For this purpose, it presented data on the subsequent therapies summarized for both treatment arms. For the global cohort, it showed the data of the first data cut-off of 24 April 2018. Table 1 shows the company's data on the subsequent therapies from its comments. For the global cohort, the company's information was supplemented by the data of the second data cut-off of 24 January 2019. Table 2 presents the subsequent therapies separately for the individual treatment arms in the cohorts.

Table 1: Information on antineoplastic therapies in the cohorts – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**		
	IMpower133 – global cohort (data cut-off: 24 January 2019) N = 403	**IMpower133 – global cohort (data cut-off: 24 April 2018) N = 403**	**IMpower133 – China (data cut-off: 29 October 2018) N = 110**
Patients with at least one subsequent therapy	235 (56.3)	220 (54.6)	64 (58.2)
Total number of treatments/lines	369	314	105
Therapy type			
Chemotherapy + non-anthracycline	185 (45.9)	169 (41.9)	60 (54.5)
Chemotherapy + anthracycline	89 (22.1)	77 (19.1)	0 (0)
Immunotherapy	24 (6.0)	21 (5.2)	1 (0.9)
Targeted therapy	3 (0.7)	3 (0.7)	11 (10.0)
Biological drug	0 (0)	0 (0)	1 (0.9)
Other	6 (1.5)	4 (1.0)	3 (2.7)

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

Table 2: Information on antineoplastic subsequent therapies in the treatment arms of the cohorts – RCT, direct comparison: atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**			
	IMpower133 – global cohort (data cut-off: 24 January 2019)		**IMpower133 – China (data cut-off: 29 October 2018)**	
	Atezolizumab + carboplatin + etoposide **N = 201**	**Placebo + carboplatin + etoposide** **N = 202**	**Atezolizumab + carboplatin + etoposide** **N = 57**	**Placebo + carboplatin + etoposide** **N = 53**
Patients with at least one subsequent therapy	110 (54.7)	125 (61.9)	32 (56.1)	32 (60.4)
Therapy type				
Chemotherapy + non-anthracycline	86 (42.8)	99 (49.0)	31 (54.4)	29 (54.7)
Chemotherapy + anthracycline	38 (18.9)	51 (25.2)	0 (0)	0 (0)
Immunotherapy	7 (3.5)	17 (8.4)	1 (1.8)	0 (0)
Targeted therapy	2 (1.0)	1 (0.5)	2 (3.5)	9 (17.0)
Biological drug	0 (0)	0 (0)	0 (0)	1 (1.9)
Other	3 (1.5)	3 (1.5)	2 (3.5)	1 (1.9)

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

In its comments, the company explained that about one fifth of the patients in the global cohort had received an anthracycline, but no patient of the cohort in China. 10% of patients in the cohort in China, in contrast, received targeted therapies, but only 0.7% of the patients in the global cohort. It attributes the latter to the clearly different genomic profile of the small cell lung cancer in Chinese patients compared to Western patients.

The company's reasoning is insufficient. In the targeted therapies, for instance, there are equally large differences between the treatment arms in the cohort in China (see Table 2). The presented data permit no conclusion on whether the differences in the subsequent therapies must be attributed to a different genomic profile. Differences in health care that might also become apparent when looking in isolation at another country within the global cohort must also be considered. Moreover, the subgroup analyses conducted by the company for the outcomes on efficacy showed no statistically significant effect modification by the characteristic "family origin". None of the conducted meta-analyses on the joint consideration of the global cohort and the cohort in China showed a statistically significant heterogeneity between the results. Therefore, the data presented by the company do not change the assessment of dossier assessment A19-86.

2.2 Assessment of the data presented on treatment discontinuations due to AEs

In its dossier, the company presented several operationalizations on the outcome "discontinuation due to AEs". However, a comparative analysis with effect estimate is only available for the operationalization "discontinuation of at least 1 component". This was used in the dossier assessment. With its comments, the company presented an individual list of the AEs that resulted in discontinuation, for instance, by providing information on the treatment phase (induction or maintenance treatment), on the investigator's assessment of the causal relation between AEs and the individual treatment components as well as on the components that had been discontinued. With these data, the company argues that the statistically significant difference to the disadvantage of atezolizumab + carboplatin + etoposide is not patient-relevant, because in most cases only the additional administration of atezolizumab or placebo had been discontinued.

Combination treatments basically involve different possibilities for the operationalization of the outcome "discontinuation due to AEs". It is possible to operationalize the outcome as "discontinuation of at least 1 treatment component". This means that a patient is considered to have an event if he or she discontinues at least part of the combination treatment due to an AE. Moreover, operationalization is conceivable as discontinuation of all components. In this case, discontinuation would not be considered an event before the discontinuation of the last treatment component.

For the benefit assessment, the outcome "discontinuation due to AEs" was regarded as operationalization of patient-relevant AEs that result in an intolerance of the current treatment. Discontinuation of the treatment or a component of the treatment thus is an indicator for these relevant AEs. Against this background, it is less relevant which or how many of the components of the treatment the patients discontinued, particularly since this is always accompanied by an unverifiable causal analysis of the AEs for the individual components. Therefore, the primary relevant factor is the fact that they discontinue a therapy. This is best represented by operationalizing at least one drug component as a discontinuation.

The data presented by the company do not challenge this approach.

2.3 Assessment of the presented meta-analysis of the global cohort and the cohort in China

2.3.1 Data presented by the company

In its dossier, the company did not use the results of the cohort in China for the derivation of an added benefit, but presented the results as supplementary information. In the dossier and in its comments, the company justified this with regulatory reasons and different research questions of the two cohorts (efficacy and safety in a global population or in a population in China and Taiwan). Due to different research questions of the cohorts, a meta-analysis was not considered meaningful. On the other hand, the company cited differences in the baseline characteristics such as ethnic origin, age group distribution, gender distribution, Eastern

Cooperative Oncology Group Performance Status (ECOG PS) and smoking status. There were also differences between the cohorts in the subsequent therapies, which could be explained by the different genomic profile of the small cell lung cancer (SCLC) in Chinese patients compared to Western patients (see above). However, with its comments, the company has now presented meta-analyses of the two cohorts of IMpower133 including subgroup analyses.

The company's reasoning was not shared. An effect modification by the characteristic "family origin" was not shown for the outcomes on efficacy in the subgroup analyses performed by the company. The company did not investigate this characteristic for the outcomes on side effects. However, none of the meta-analyses conducted on the joint consideration of the global cohort and the cohort in China showed a statistically significant heterogeneity between the results. This implies that the inclusion of the cohort in China did not result in a decisive effect modification.

In principle, it would be more appropriate to jointly analyse the data of both cohorts on the basis of individual patient data (IPD). However, the company presented no such analyses.

Data cut-offs and outcomes

For the meta-analysis of the two cohorts of the IMpower133 study (global cohort and cohort in China), the company used the last data cut-off of 31 July 2019 for the cohort in China. According to the company, the approval in China was based on this data cut-off. This approach is appropriate.

For the global cohort, the company used the data cut-off of 24 April 2018. From the company's point of view, this data cut-off presented the basis for the final analysis and thus the relevant one. The later data cut-off of 24 January 2019 was said to be explorative. Deviating from the company, the data cut-off of 24 January 2019 was used for the benefit assessment, since this data cut-off was requested by the European Medicines Agency (EMA) within the framework of the approval and there was no indication that it was conducted in a results-driven manner. Moreover, it provided more information as a later analysis.

With its comments, the company presented no new analyses on the outcomes on morbidity (symptoms and health status) and health-related quality of life.

Analyses on subgroup characteristics

In its dossier, the company only presented subgroup analyses for the global cohort. For the outcomes on side effects only analyses for the characteristics "age" and "sex" were available out of the relevant subgroup characteristics ("age", "sex", "family origin", "smoking status", "brain metastases"). With its comments, the company also presented subgroup analyses for the cohort in China; however, for the outcomes on side effects it only presented subgroup analyses on the characteristics "age" and "sex" out of the relevant characteristics.

2.3.2 Treatment and observation duration of the outcomes

Table 3 shows the mean / median treatment duration of patients and the median observation time for individual outcomes for the data cut-off of 31 July 2019 for the cohort in China subsequently submitted by the company as well as for the data cut-offs of 24 April 2018 and 24 January 2019 from the company's dossier for the global cohort.

Table 3: 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
Impower133 (cohort in China)	N[a] = 57	N[a] = 53
Treatment duration [months]		
Median [min; max][d]	3.7 [0.0; 23.0]	3.7 [1.0; 12.0]
Mean (SD)[d]	5.5 (4.9)	4.2 (2.1)
Observation period [months]		
Overall survival		
Median [min; max][d]	21.9 [0.0; 24.5]	20.5 [0.9; 26.5]
Mean (SD)	ND	ND
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.
d. Data cut-off: 31 July 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 treatment groups, nor relevant differences in the treatment duration/observation period between the two cohorts IMpower133 study.

2.3.3 Risk of bias

The data subsequently submitted have not changed the risk of bias across outcomes and the outcome-specific risk of bias of the results of the IMpower133 study. As described in dossier assessment A19-86, the risk of bias of the results on the outcome "overall survival" was rated as low.

The risk of bias of each of the results of the outcomes serious adverse events (SAEs) and severe AEs is rated as high.

The risk of bias of the results for the outcome "discontinuation due to AEs" is rated as low; however, the certainty of results for this outcome was assumed to be restricted (see dossier assessment A19-86).

2.3.4 Results of the meta-analyses

Table 4 summarizes the results of the meta-analyses on 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 supplement the data from the company's dossier and comments. In Appendix A, the results of the meta-analyses are presented in the form of Forest plots. The Kaplan-Meier curves on the cohort in China provided by the company (data cut-off: 31 July 2019) are found in Appendix B.

Table 4: Results (mortality, side effects, time to event) – RCT, direct comparison: atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide (multipage table)

Outcome category **Outcome** **Study**	**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 (31 July 2019)	57	11.4 [8.8; 15.4] 41 (71.9)	53	11.9 [10.0; 14.7] 41 (77.4)	0.93 [0.60; 1.43]; 0.734
Total[b]					0.79 [0.65; 0.97]; 0.026
Side effects					
AEs (supplementary information)					
IMpower133 (24 April 2018)	198	ND 198 (100)	196	ND 189 (96.4)	–
IMpower133 – China (31 July 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 (31 July 2019)	57	ND 21 (36.8)	52	ND 14 (26.9)	1.36 [0.69; 2.69]; 0.370
Total[c]					1.16 [0.86; 1.56]; ND
Severe AEs (CTCAE grade 3 or 4)					
IMpower133 (24 April 2018)	198	ND 136 (68.7)[d]	196	ND 136 (69.4)[d]	1.07 [0.84; 1.37]; 0.570
IMpower133 – China (31 July 2019)	57	ND 46 (80.7)	52	ND 43 (82.7)	1.06 [0.69; 1.62]; 0.784
Total[c]					1.07 [0.86; 1.32]; ND
Discontinuation due to AEs[e]					
IMpower133 (24 April 2018)	198	ND 22 (11.1)	196	ND 6 (3.1)	3.42 [1.38; 8.48]; 0.005
IMpower133 – China (31 July 2019)	57	ND 7 (12.3)	52	ND 0 (0)	NC[f]; 0.010
Total					NC

Table 4: Results (mortality, side effects, time to event) – RCT, direct comparison: atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide (multipage table)

Outcome category Outcome Study	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]
a. For overall survival: 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. For the outcomes on side effects: effect and CI: Cox model, unstratified; p-value: unstratified log-rank test. b. Meta-analysis with fixed effect; Institute's calculation. c. Company's meta-analysis with fixed effect. d. 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. e. Discontinuation of at least one treatment component. f. Since no events occurred in the placebo arm, the HR cannot be estimated. AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; 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 on side effects. A hint can be determined for the outcome "overall survival".

Mortality

Overall survival

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. This resulted in an indication of an added benefit of atezolizumab in combination with carboplatin and etoposide in comparison with carboplatin and etoposide.

The global cohort shows an effect modification for the characteristic "age". However, by adding the cohort in China, for which the company had subsequently submitted subgroup analyses; the overall consideration shows no effect modification (see Table 8 in Appendix C).

Side effects

SAEs, severe AEs (Common Terminology Criteria for Adverse Events [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 a hint of greater harm from atezolizumab in combination with carboplatin and etoposide in comparison with carboplatin + etoposide for this outcome.

Subgroups and other effect modifiers

Only results involving an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) were presented. In addition, subgroup results were only presented if there was a statistically significant and relevant effect in at least one subgroup.

The subgroup analyses presented by the company with the comments involved no effect modifications with statistically significant interactions.

2.3.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are deduced below. Taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the General Methods of IQWiG [4].

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.

2.3.5.1 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 the present addendum and dossier assessment A19-86 (see the following Table 5).

Table 5: 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	Median: 12.3 and 11.4 vs. 10.3 and 11.9 HR: 0.79 [0.65; 0.97]; p = 0.026 probability: “indication”	Outcome category: mortality $0.95 \leq CI_u < 1.00$ Added benefit, extent: “minor”
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 5: 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 5: 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 data	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 [0.86; 1.56]; p = ND	greater/lesser harm not proven
Severe AEs (CTCAE grade 3–4)	Median: ND vs. ND HR: 1.07 [0.86; 1.32]; p = ND	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 5: 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 a statistically significant and relevant effect is present.
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 p-value serves for the assessment of the extent. Due to the proximity of the p-value to the significance threshold of 0.05, the extent is estimated to be "minor".

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

Table 6 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 6: Positive and negative effects from the assessment of atezolizumab + carboplatin + etoposide in comparison with placebo + carboplatin + etoposide

Positive effects	**Negative effects**
Mortality ▪ **Overall survival: indication of added benefit – extent: "minor"**	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: minor"
Results printed in **bold** result from the analyses subsequently submitted by the company with the written comments. AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events; SAE: serious adverse events	

The overall consideration shows one positive effect and several negative effects under consideration of the data subsequently submitted. On the side of positive effects, there was an indication of minor added benefit for the outcome "overall survival". This is contrasted by negative effects for the outcomes on non-serious/non-severe side effects as well as serious/severe side effects, in each case with a probability "hint" and an extent of "minor to considerable". However, the negative effects do not completely challenge the positive effect on overall survival, so that in summary, an added benefit of atezolizumab in combination with carboplatin and etoposide versus carboplatin and etoposide yields an indication of a minor added benefit for adult patients with ES-SCLC.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure have changed the conclusion on the added benefit of atezolizumab in combination with carboplatin and etoposide from dossier assessment A19-86.

The following Table 7 shows the result of the benefit assessment of atezolizumab in combination with carboplatin and etoposide under consideration of dossier assessment A19-86 and the present addendum.

Table 7: 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	Indication of minor added benefit

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 G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Atezolizumab (kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag: A19-86 [online]. 13.01.2020 [Accessed: 15.01.2020]. (IQWiG-Berichte; Volume 686). URL: https://www.iqwig.de/download/A19-86_Atezolizumab_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. Roche Pharma. Atezolizumab (Tecentriq): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 02.10.2019 [Accessed: 15.01.2020]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/503/.

3. Roche Pharma. Stellungnahme zum IQWiG-Bericht Nr. 868: Atezolizumab (kleinzelliges Lungenkarzinom); Nutzenbewertungen gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-86. 2020. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/503/#beschluesse im Dokument "Zusammenfassende Dokumentation"].

4. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 01.07.2019]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

Appendix A – Forest plots on the meta-analyses

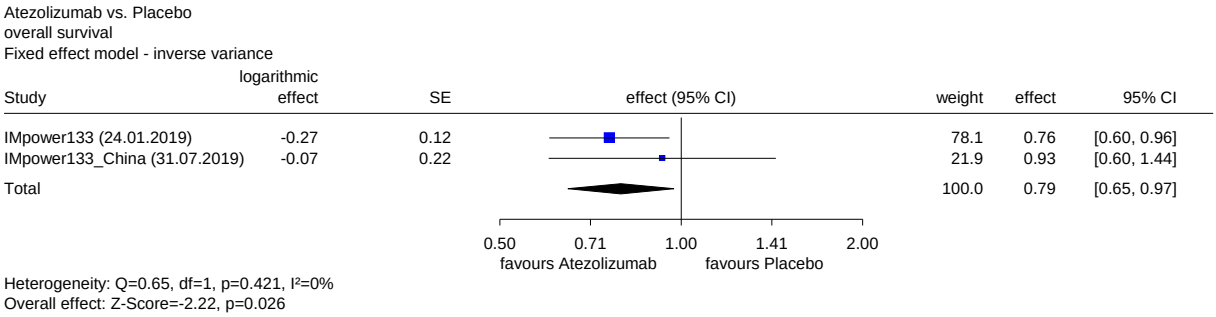


Figure 1: Meta-analysis for the outcome “overall survival”; study IMpower133: Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide; effect measure: HR

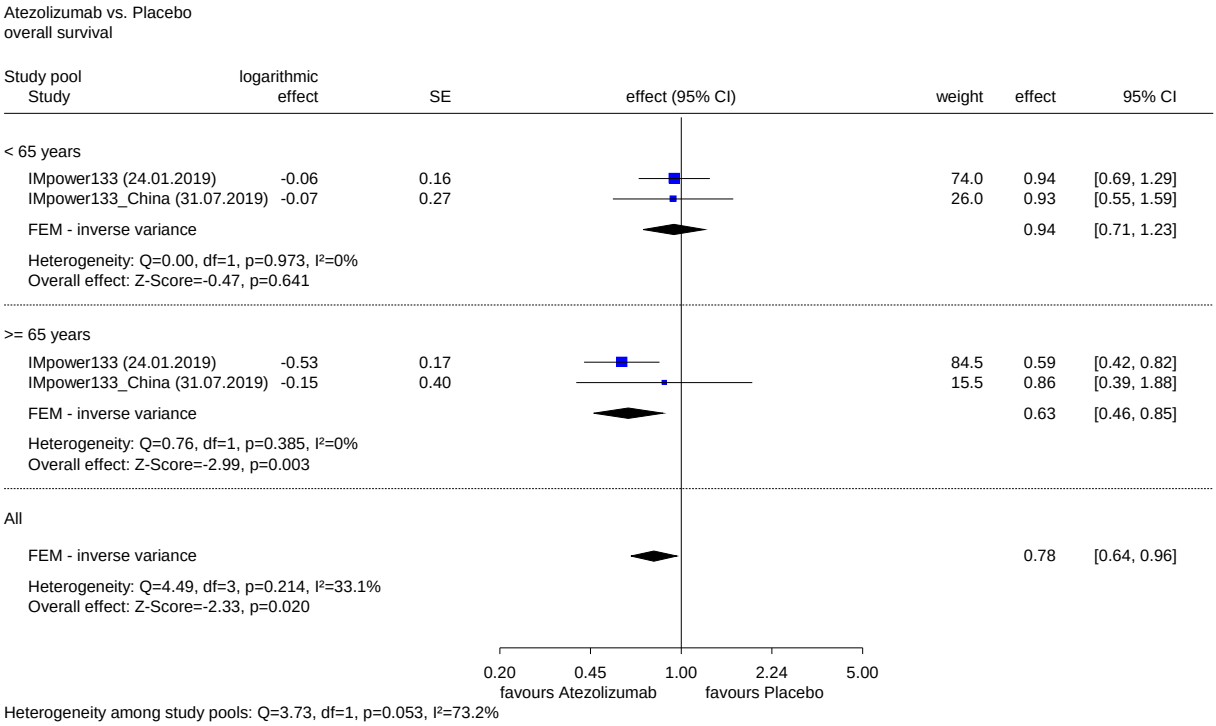
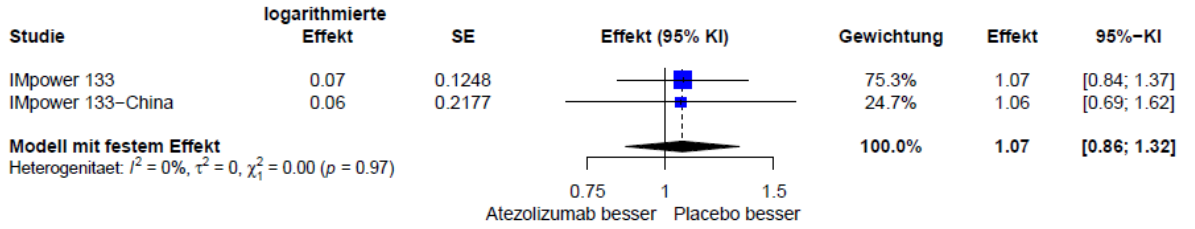
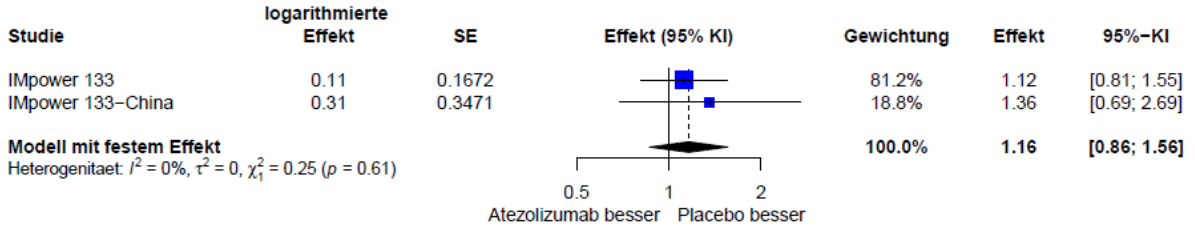


Figure 2: Subgroup analysis by the characteristic “age” for the outcome “overall survival”; study IMpower133: Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide; effect measure: HR



Studie: Study; logarithmierte Effekt: logarithmic effects; Effekt: effect; Gewichtung: weight; 95% KI: 95% CI; Modell mit festem Effekt: fixed-effect model; Heterogenität: heterogeneity; Atezolizumab besser: favours atezolizumab; Placebo besser: favours placebo

Figure 3: Meta-analysis for the outcome “severe AEs” (CTCAE grade 3–4); study IMpower133: Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide; effect measure: HR



Studie: Study; logarithmierte Effekt: logarithmic effects; Effekt: effect; Gewichtung: weight; 95% KI: 95% CI; Modell mit festem Effekt: fixed-effect model; Heterogenität: heterogeneity; Atezolizumab besser: favours atezolizumab; Placebo besser: favours placebo

Figure 4: Meta-analysis for the outcome “SAEs”; study IMpower133: Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide; effect measure: HR

Appendix B – Kaplan-Meier curves on results of the Impower133 study

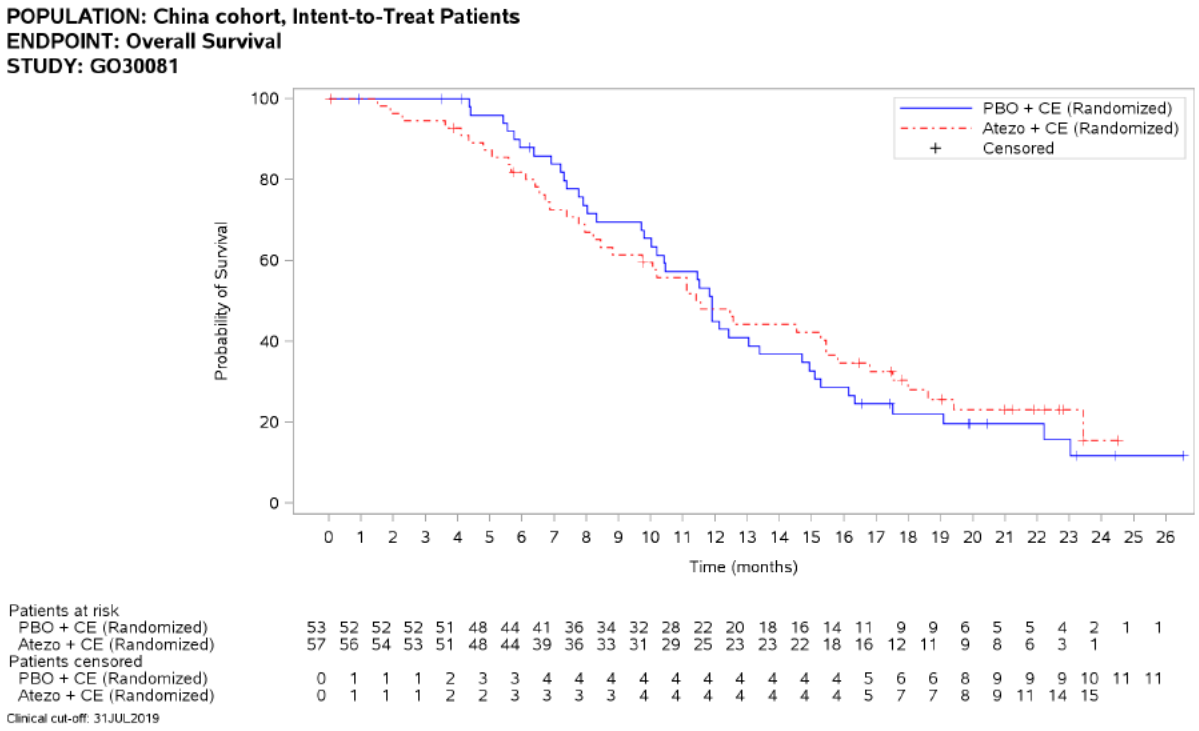


Figure 5: Kaplan-Meier curves for the outcome “overall survival”; study IMpower133: Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide; cohort in China, data cut-off: 31 July 2019

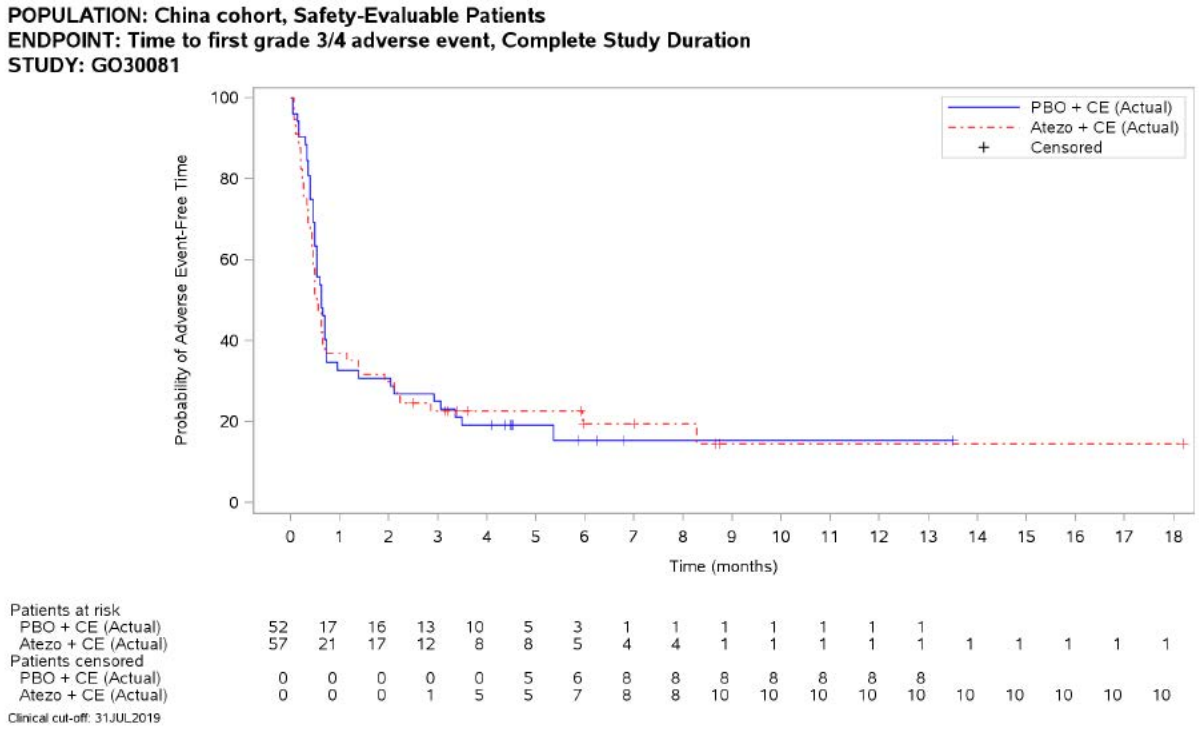


Figure 6: Kaplan-Meier curves for the outcome “severe AEs” (CTCAE grade 3–4); study IMpower133: Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide; cohort in China, data cut-off: 31 July 2019

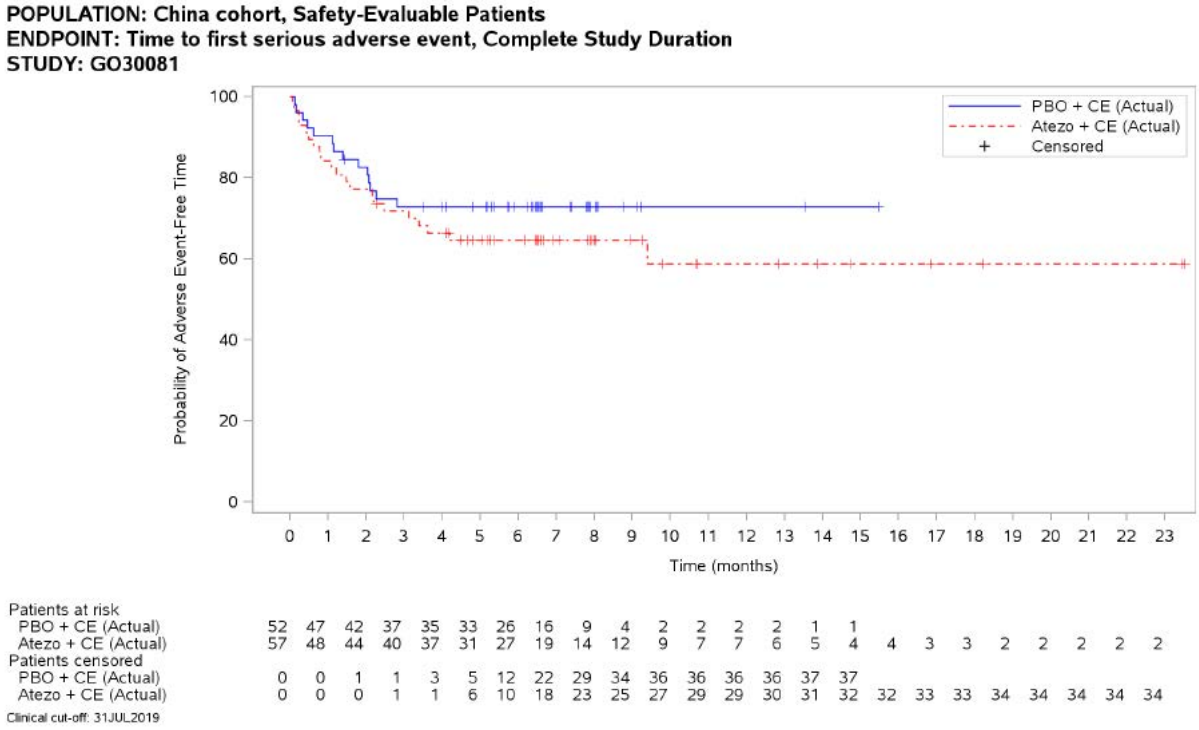


Figure 7: Kaplan-Meier curves for the outcome “SAEs”; study IMpower133: Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide; cohort in China, data cut-off: 31 July 2019

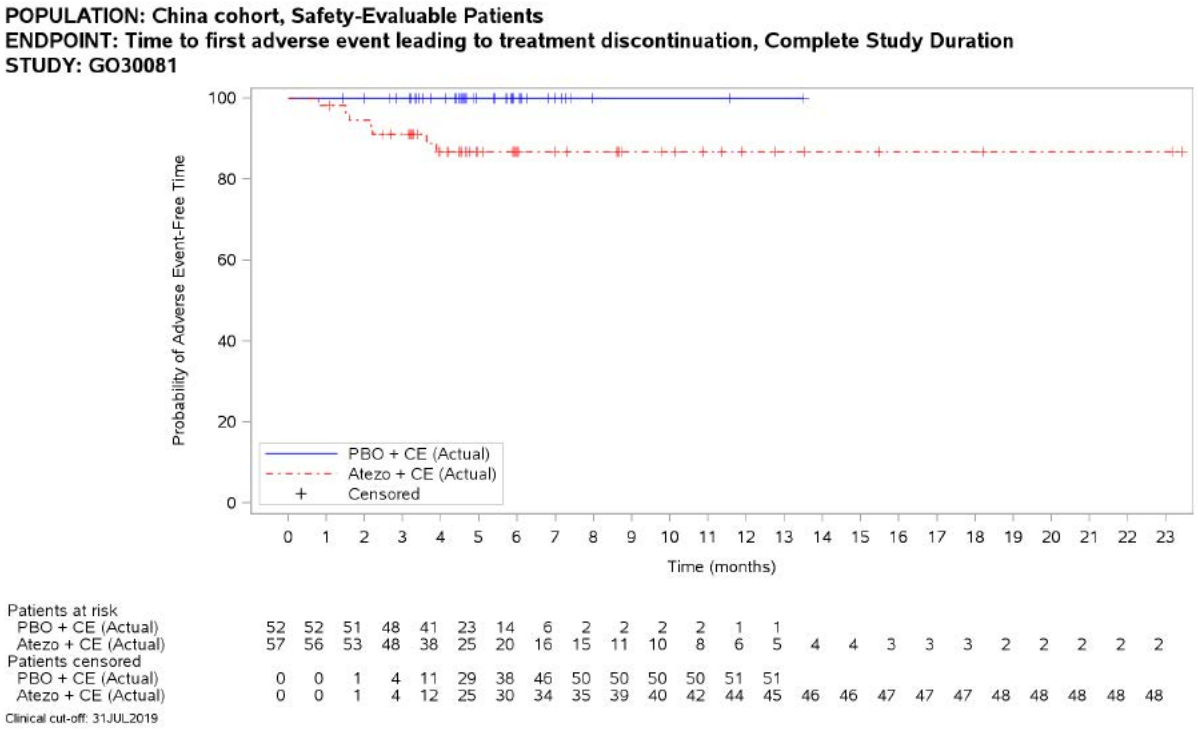


Figure 8: Kaplan-Meier curves for the outcome “discontinuation due to AEs”; study IMpower133: Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide; cohort in China, data cut-off: 31 July 2019

Appendix C – Subgroup analyses by the characteristic "age" for the outcome "overall survival"

Table 8: Subgroups (mortality, time to event) – RCT, direct comparison: atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide

Outcome category Outcome Characteristic Study Subgroup	Atezolizumab + carboplatin + etoposide N	Atezolizumab + carboplatin + etoposide Median time to event in months [95% CI] Patients with event n (%)	Placebo + carboplatin + etoposide N	Placebo + carboplatin + etoposide Median time to event in months [95% CI] Patients with event n (%)	Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide HR [95% CI][a]	 p-value[b]
Mortality						
Overall survival						
Age						
IMpower133 (24 January 2019)						
< 65 years	111	12.1 [9.7; 15.4] 78 (70.3)	106	11.5 [9.5; 13.5] 79 (74.5)	0.94 [0.68; 1.28]	0.678
≥ 65 years	90	14.4 [10.6; 17.8] 64 (71.1)	96	9.6 [8.4; 10.7] 81 (84.4)	0.59 [0.42; 0.82]	0.002
IMpower133 – China (31 July 2019)						
< 65 years	41	11.4 [8.4; 15.4] 29 (70.7)	35	11.5 [8.3; 14.9] 26 (74.3)	0.93 [0.54; 1.57]	0.775
≥ 65 years	16	15.4 [7.4; 18.0] 12 (75.0)	18	12.4 [9.7; 15.3] 15 (83.3)	0.86 [0.39; 1.86]	0.696
Total					Interaction[c]:	0.053
< 65 years[d]					0.94 [0.71; 1.23]	0.641
≥ 65 years[d]					0.63 [0.46; 0.85]	0.003

a. Unstratified Cox regression model.
b. p-value for the effect estimate from log-rank test.
c. Institute's calculations, p-value from Q test for heterogeneity.
d. Institute's calculation: meta-analysis with fixed effect.

CI: confidence interval; HR: hazard ratio; n: patients with event; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus