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Atezolizumab (non-small cell lung cancer) –

Addendum to Commission A17-50[1]

Addendum

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Abbreviation	Meaning
AE	adverse event
CSR	clinical study report
ECOG PS	Eastern Cooperative Oncology Group Performance Status
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)
NSCLC	non-small cell lung cancer
RCT	randomized controlled trial
RR	relative risk

1 Background

On 5 February 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-50 (Atezolizumab [non-small cell lung cancer] – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier on atezolizumab, the pharmaceutical company (hereinafter referred to as "the company") had included the OAK study in its study pool, but not the POPLAR study, which is also relevant in the therapeutic indication [2]. After the oral hearing [3], the company submitted analyses on the POPLAR study and meta-analyses based on individual patient data (IPD) of the studies OAK and POPLAR [4].

With its written comments [5], the company had already subsequently submitted data for the OAK study on immune-related adverse events (AEs).

The G-BA commissioned IQWiG with the assessment of the POPLAR study and with the assessment of the analyses on immune-related AEs of the OAK study subsequently submitted.

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

The data subsequently submitted by the company refer to the studies OAK and POPLAR. Both studies investigated the comparison of atezolizumab versus docetaxel in adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with disease progression during or after platinum-based chemotherapy for advanced disease. Both studies were therefore relevant for research question 1 of dossier assessment A17-50 on atezolizumab (patients for whom treatment with docetaxel, pemetrexed or nivolumab is indicated [1]).

However, the data presented by the company on the POPLAR study were incomplete and overall not usable even under consideration of the analyses subsequently submitted after the oral hearing. This is explained in detail in Section 2.1.

The data on immune-related AEs of the OAK study submitted subsequently are assessed in Section 2.2.

Section 3 summarizes the results of the assessment of atezolizumab under consideration of dossier assessment A17-50 and the present addendum.

2.1 Data presented on the POPLAR study

The POPLAR study was an open-label phase 2 randomized controlled trial (RCT), which compared atezolizumab with docetaxel. The inclusion criteria largely concurred with those of the OAK study. Both studies included adult patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC with disease progression during or after platinum-based chemotherapy (no more than 2 lines of treatment of cytotoxic chemotherapy) for advanced disease. Another inclusion criterion was an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, and hence good general condition of the participants.

In the POPLAR study, 287 patients were randomly allocated to the study arms, 144 patients to the atezolizumab arm and 143 patients to the docetaxel arm. Hence it was markedly smaller than the OAK study (1225 participants in total) and comprised about 19% of the patients relevant for research question 1.

Primary outcome of the studies OAK and POPLAR was overall survival. Patient-relevant secondary outcomes were symptoms, health-related quality of life, and AEs.

A detailed description of the characteristics of the study and of the interventions of the POPLAR study can be found in dossier assessment A17-50 [1].

Based on the information provided by the company, 3 data cut-offs[2] in particular can be differentiated for the POPLAR study:

[2] Module 5 of the dossier contains an additional short report on another data cut-off from 1 December 2015 described as “explorative”. This report presents results on overall survival; further analyses are missing.

- Data cut-off from 30 January 2015 (after 150 deaths): This data cut-off was defined as final data cut-off in the original study protocol. Knowing the data on this data cut-off ([6], protocol version 6 from 24 February 2015), the number of required deaths was increased to 180 and the data cut-off from 30 January 2015 was subsequently classified as "third data cut-off" [7]. The clinical study report (CSR) of the POPLAR study on the data cut-off from 8 May 2015 contains individual pieces of information on this data cut-off (see below for details).
- Data cut-off from 8 May 2015 (after 180 deaths): This data cut-off corresponds to the "primary" data cut-off newly defined in the protocol version 6 mentioned above. After the oral hearing, the company subsequently submitted analyses on this data cut-off (see below for details). In addition, Module 5 of the original dossier contains a CSR on this data cut-off [7].
- Data cut-off from 7 April 2017: The reason for this data cut-off is unclear. Neither the CSR of the POPLAR study, nor the study protocol, nor the documents subsequently submitted by the company contain information on the reasons why the POPLAR data were analysed at this time point. It is also unclear whether additional analyses on other data cut-offs were conducted. After the oral hearing, the company subsequently submitted analyses on the data cut-off from 7 April 2017 (see below for details). A CSR on this data cut-off is not available.

For all 3 data cut-offs mentioned, the data subsequently submitted by the company are incomplete. This applies both to the POPLAR study itself and the meta-analyses of the studies POPLAR and OAK. The following tables Table 1 (POPLAR study) and Table 2 (meta-analyses) provide an overview of the available information.

Table 1: Overview of the analyses on the POPLAR study subsequently submitted by the company

Outcome category (outcomes)	**Original final data cut-off ("third interim analysis") (30 January 2015)[a]**	**"Primary" data cut-off after protocol change (8 May 2015)[b]**	**Last available data cut-off (7 April 2017)[b]**
Mortality (overall survival)	-[c]	Available (including subgroup analyses)	Available (including subgroup analyses)
Morbidity (responder analyses EORTC QLQ-C30 and LC13)	-	Available (including subgroup analyses)	Available (including subgroup analyses)
Health-related quality of life (responder analyses EORTC QLQ-C30)	-	Available (including subgroup analyses)	Available (including subgroup analyses)
Superordinate AE outcomes (overall rates of SAEs, severe AEs [CTCAE ≥ 3], discontinuations due to AEs)	-	-[d]	Available (including subgroup analyses)
Immune-related AEs (SAEs, severe AEs [CTCAE grade ≥ 3])	-	-[e]	-
Specific AEs (PTs and SOCs for AEs, SAEs, severe AEs [CTCAE ≥ 3], discontinuations due to AEs)	-	-[d]	▪ Available only for non-serious AEs with a difference of ≥ 2% between the treatment groups ▪ No PT/SOC analyses on SAEs, severe AEs, discontinuations due to AEs

a: The company did not subsequently submit any analyses on this data cut-off after the oral hearing.
b: The company subsequently submitted analyses on this data cut-off after the oral hearing; "available" means: data output in additional document, no processing by the company in accordance with the G-BA requirements stipulated in the dossier templates.
c: Analysis only in the CSR on the data cut-off from 8 May 2015 (Module 5 of the dossier); no analyses by the company in Module 4 of the dossier or in the documents subsequently submitted.
d: Only information on event rates in the CSR (Module 5 of the dossier); no subgroup analyses; no analyses by the company in Module 4 of the dossier or in the documents subsequently submitted.
e: Only information on event rates for severe AEs (CTCAE ≥ 3) in the CSR (Module 5 of the dossier); no subgroup analyses; no analyses by the company in Module 4 of the dossier or in the documents subsequently submitted. No data on SAEs.

AE: adverse event; CSR: clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; SAE: serious adverse event; SOC: System Organ Class

Table 2: Overview of the meta-analyses of the studies OAK (total study population) and POPLAR presented by the company

Outcome category (outcomes)	Meta-analysis OAK[a] and POPLAR (data cut-off 30 January 2015)	Meta-analysis OAK[a] and POPLAR (data cut-off 8 May 2015)[b]	Meta-analysis OAK[a] and POPLAR (data cut-off 7 April 2017)[c]
Mortality (overall survival)	-	-	Available (no subgroup analyses)
Morbidity (responder analyses EORTC QLQ-C30 and LC13)	-	-	Available (no subgroup analyses)
Health-related quality of life (responder analyses EORTC QLQ-C30)	-	-	Available (no subgroup analyses)
Superordinate AE outcomes (overall rates of SAEs, severe AEs [CTCAE ≥ 3], discontinuations due to AEs)	-	-	-
Immune-related AEs (SAEs, severe AEs [CTCAE grade ≥ 3])	-	-	-
Specific AEs (PTs and SOCs for AEs, SAEs, severe AEs [CTCAE ≥ 3], discontinuations due to AEs)	-	-	-

a: N = 1225, data cut-off: 23 January 2017.
b: For the data cut-off from 8 May 2015 of the POPLAR study, the company presented only meta-analyses in connection with the subpopulation of the OAK study at the data cut-off from 7 July 2016. This data cut-off is not relevant for the present assessment (see dossier assessment A17-50 [1]). Irrespective of this, these meta-analyses are also incomplete.
c: The company subsequently submitted analyses on this data cut-off after the oral hearing; "available" means: data output in additional document, no processing by the company in accordance with the G-BA requirements stipulated in the dossier templates.
AE: adverse event; CSR: clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; SAE: serious adverse event; SOC: System Organ Class

In summary, both the data on the POPLAR study presented by the company and the meta-analyses of the studies POPLAR and OAK are incomplete and overall not usable. Irrespective of their individual principal suitability, this applies to all 3 considered data cut-offs of the POPLAR study.

The data on the POPLAR study on the last data cut-off from 7 April 2017 subsequently submitted after the oral hearing are presented as additional information in Appendix A. The available information is largely consistent with the results of the OAK study, also regarding the

subgroup results according to PD-L1 status. Hence an assessment based on the results of the OAK study is still possible.

2.2 Data on immune-related AEs of the OAK study subsequently submitted

Dossier assessment A17-50 used relative risks (RRs) based on event rates for specific AEs (including immune-related AEs) because no time-adjusted analyses were available in the presence of different observation periods. This was possible for the constellation present in the OAK study (see dossier assessment A17-50 [1]).

With its written comments, the company presented time-adjusted analyses on AEs, but only selectively on immune-related AEs (including severe and serious immune-related AEs) [5]. Such a selective change of the type of analysis only for individual AEs is susceptible to bias and therefore not meaningful. The conclusions are therefore still drawn on the basis of the RRs.

However, the event rates on serious immune-related AEs, which were not available in the dossier itself, can also be inferred from the data presented by the company. According to these data, a total of 36 (5.9%) patients in the atezolizumab arm, and 2 (0.3%) patients in the docetaxel arm had a serious immune-related AE (RR: 17.08 [4.13; 70.63]; $p < 0.001$) in the relevant total study population of the OAK study (N = 1225) at the second data cut-off from 23 January 2017. The result is consistent with the result for severe immune-related AEs, supporting at outcome level the indication of greater harm of major extent of atezolizumab versus docetaxel in these specific AEs. This does not change the overall conclusion on atezolizumab.

3 Summary

The additional analyses of the POPLAR study and the additional data on immune-related AEs of the OAK study do not change the conclusion on the added benefit of atezolizumab versus the appropriate comparator therapy in comparison with dossier assessment A17-50.

The following Table 3 shows the result of the benefit assessment of atezolizumab.

Table 3: Atezolizumab – probability and extent of added benefit

Research question[a]	**Subindication**[a]	**ACT**[b]	**Probability and extent of added benefit**[c]
1	Adult patients with locally advanced or metastatic NSCLC after prior chemotherapy for whom treatment with docetaxel, pemetrexed or nivolumab is indicated[d]	**Docetaxel**, pemetrexed[e] or nivolumab	Patients with: ▪ high PD-L1 status (TC3 or IC3): indication of a major added benefit ▪ low PD-L1 status (TC0/1/2 and IC0/1/2): indication of a non-quantifiable added benefit
2	Adult patients with locally advanced or metastatic NSCLC after prior chemotherapy for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated[d]	Best supportive care[f]	Added benefit not proven

a: It is assumed for the present therapeutic indication that the NSCLC patients are in disease stage IIIB to IV (staging according to IASLC, UICC), without indication for curative resection, radiotherapy or radiochemotherapy. Treatment is palliative. After completion of the first-line treatment, subsequent therapy depends on the course of disease, general condition, success and tolerability of the first-line treatment, accompanying diseases, tumour histology, activating mutations and the patient's treatment request.

b: 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**.

c: Changes in comparison with dossier assessment A17-50 are printed in bold.

d: Patients with activating EGFR mutations or ALK translocations should have received therapy targeted to these mutations before receiving atezolizumab.

e: Except in mainly squamous histology.

f: Best possible supportive therapy, optimized for the individual patient, for alleviation of symptoms and improvement in the quality of life.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; IC: immune cells; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; TC: tumour cells; UICC: Union for International Cancer Control

The G-BA decides on the added benefit.

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Appendix A – Results of the POPLAR study

Table 4: Characteristics of the study population of the POPLAR study

Study Characteristics Category	Atezolizumab	Docetaxel
Study POPLAR	N[a] = 144	N[a] = 143
Age [years], mean (SD)	61.5 (9.2)	61.8 (9.4)
Sex [F/M], %	35/65	47/53
Ethnicity, n (%)		
Asian	23 (16.0)	13 (9.1)
White	110 (76.4)	116 (81.1)
Other[b]	11 (7.6)	14 (9.8)
Region, n (%)		
North America	70 (48.6)	67 (46.9)
Europe[c]	56 (38.9)	63 (44.1)
Asia	18 (12.5)	13 (9.1)
Smoking status, n (%)		
Never-smoker	27 (18.8)	29 (20.3)
Smoker (current or former)	117 (81.3)	114 (79.7)
ECOG Performance Status, n (%)		
0	46 (32.4)	45 (31.7)
1	96 (67.6)	97 (68.3)
Histology, n (%)		
Squamous	49 (34.0)	48 (33.6)
Non-squamous	95 (66.0)	95 (66.4)
Prior therapies, n (%)		
1	93 (64.6)	96 (67.1)
2	51 (35.4)	47 (32.9)
Current disease status, n (%)		
Locally advanced	8 (5.6)	5 (3.5)
Metastatic disease	136 (94.4)	138 (96.5)
Number of metastases at start of study, mean (SD)	2.97 (1.38)	3.10 (1.39)
Liver metastases at start of study, n (%)	33 (22.9)	33 (23.1)
Bone metastases at start of study, n (%)	35 (24.3)	46 (32.2)
Brain metastases at start of the study, n (%)	8 (5.6)	15 (10.5)
EGFR mutation status[d], n (%)		
Positive	11 (7.6)	8 (5.6)
Negative	72 (50.0)	75 (52.4)
Unknown	61 (42.4)	60 (42.0)

(continued)

Table 4: Characteristics of the study population of the POPLAR study (continued)

Study Characteristics Category	**Atezolizumab**	**Docetaxel**
Study POPLAR	N[a] = 144	N[a] = 143
ALK translocation status[d], n (%)		
Positive	0	3 (2.1)
Negative	61 (42.4)	55 (38.5)
Unknown	83 (57.6)	85 (59.4)
PD-L1 status, n (%)		
TC3 or IC3	24 (16.7)	23 (16.1)
TC0/1/2 and IC0/1/2	120 (83.3)	120 (83.9)
Treatment discontinuation[e], n (%)	ND	ND
Study discontinuation[f], n (%)	ND	ND

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: Contains the categories of American Indians or native Alaskans, African Americans, native Hawaiians or Pacific Islanders.
c: Including Turkey.
d: Taking a test for the determination of the respective mutation status was not a compulsory prerequisite for inclusion in the study.
e: Data cut-off from 8 May 2015: treatment discontinuation in the atezolizumab arm 118 (81.9%), docetaxel arm 134 (93.7%). Percentages: Institute's calculation.
f: Data cut-off from 8 May 2015, study discontinuation (including deaths, discontinuation by patient, lost to follow-up): atezolizumab arm 84 (58.3%), docetaxel arm 106 (74.1%).

ALK: anaplastic lymphoma kinase; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; F: female; IC: immune cells; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; PD-L1: programmed cell death ligand 1; SD: standard deviation; TC: tumour cells

Table 5: Results of the POPLAR study at the data cut-off 7 April 2017

Study	Atezolizumab		Docetaxel		Atezolizumab vs. docetaxel
Outcome category Outcome	**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]**
POPLAR					
Mortality					
Overall survival	144	12.6 [9.7; 16.2] 115 (70.9)	143	9.7 [8.6; 12.0] 119 (83.2)	0.76 [0.58; 0.999]; 0.046
Morbidity					
Symptoms (EORTC QLQ-C30 symptom scales) – time to deterioration[b]					
Nausea and vomiting	138	8.3 [4.1; 20.8] 60 (43.5)	132	3.6 [2.9; 5.4] 57 (43.2)	0.63 [0.43; 0.94]; 0.029
Diarrhoea	139	11.8 [4.2; NC] 54 (38.8)	130	3.7 [3.1; NC] 50 (38.5)	0.74 [0.49; 1.11]; 0.145
Appetite loss	138	2.2 [1.5; 5.6] 78 (56.5)	132	3.8 [2.2; 7.2] 58 (43.9)	1.19 [0.83; 1.70]; 0.351
Dyspnoea	139	3.7 [2.2; 6.2] 76 (54.7)	132	3.0 [2.8; 4.9] 58 (43.9)	0.89 [0.61; 1.30] 0.554
Fatigue	139	2.1 [1.5; 3.0] 91 (65.5)	132	1.5 [1.4; 2.1] 87 (65.9)	0.75 [0.54; 1.04]; 0.084
Insomnia	138	6.9 [3.0; 15.5] 62 (44.9)	131	7.5 [2.9; NA] 51 (38.9)	0.86 [0.58; 1.28]; 0.461
Pain	139	2.1 [1.4; 3.8] 93 (66.9)	132	2.1 [1.5; 3.6] 74 (56.1)	0.95 [0.69; 1.33]; 0.777
Constipation	138	5.1 [3.0; NA] 61 (44.2)	132	3.6 [2.1; 7.1] 60 (45.5)	0.74 [0.51; 1.09]; 0.125
Symptoms (EORTC QLQ-LC13 symptom scales) – time to deterioration[b]					
Haemoptysis	134	NA [25.8; NC] 23 (17.2)	122	NA [13.0; NC] 20 (16.4)	0.73 [0.38; 1.41]; 0.350
Pain (chest)	133	10.5 [6.2; NC] 51 (38.3)	122	7.5 [5.4; 17.2] 39 (32.0)	0.78 [0.49; 1.22]; 0.273
Sore mouth	134	14.1 [11.1; 29.8] 46 (34.3)	123	2.9 [2.4; 6.9] 54 (43.9)	0.40 [0.25; 0.63]; < 0.001
Dysphagia	134	18.0 [11.2; NC] 43 (32.1)	123	NC [7.2; NC] 31 (25.2)	0.83 [0.50; 1.37]; 0.454
Neuropathy peripheral	134	16.6 [9.9; NC] 45 (33.6)	123	2.9 [2.1; 4.4] 57 (46.3)	0.38 [0.25; 0.59]; < 0.001
Alopecia	130	NA [NC; NC] 25 (19.2)	123	0.8 [0.8; 0.9] 97 (78.9)	0.04 [0.02; 0.08]; < 0.001

(continued)

Table 5: Results of the POPLAR study at the data cut-off 7 April 2017 (continued)

Study	Atezolizumab		Docetaxel		Atezolizumab vs. docetaxel
Outcome category Outcome	**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]**
POPLAR					
Symptoms (EORTC QLQ-LC13 symptom scales) – time to deterioration[b]					
Dyspnoea	134	2.1 [1.4; 2.9] 89 (66.4)	123	2.2 [1.5; 2.8] 74 (60.2)	1.00 [0.72; 1.39]; 0.994
Cough	134	3.7 [3.4; 9.7] 69 (51.5)	122	3.8 [2.3; NC] 47 (38.5)	0.98 [0.65; 1.47]; 0.927
Pain (arm/shoulder)	134	10.4 [4.2; 14.7] 59 (44.0)	121	7.5 [3.6; NC] 40 (33.1)	1.01 [0.65; 1.57]; 0.965
Pain (other)	132	3.6 [2.9; 6.3] 75 (56.8)	118	3.5 [2.8; 4.9] 57 (48.3)	0.76 [0.52; 1.12]; 0.171
Health-related quality of life					
EORTC QLQ-C30 functional scales – time to deterioration[b]					
Physical functioning	139	2.8 [2.1; 4.9] 84 (60.4)	132	3.1 [2.2; 3.7] 65 (49.2)	1.05 [0.74; 1.50]; 0.765
Emotional functioning	139	9.1 [3.7; 18.8] 64 (46.0)	130	15.8 [4.9; NC] 41 (31.5)	1.18 [0.78; 1.80] 0.431
Cognitive functioning	139	3.5 [2.2; 6.9] 73 (52.5)	130	2.9 [2.1; 3.8] 63 (48.5)	0.92 [0.65; 1.32]; 0.666
Social functioning	139	3.7 [2.2; 8.3] 72 (51.8)	130	2.9 [1.5; 4.9] 68 (52.3)	0.73 [0.51; 1.04]; 0.080
Global health status	139	2.1 [1.6; 3.5] 89 (64.0)	129	3.5 [2.1; 5.4] 58 (45.0)	1.19 [0.83; 1.69]; 0.340
Role functioning	139	1.5 [1.4; 2.4] 88 (63.3)	131	1.6 [1.4; 2.3] 79 (60.3)	0.87 [0.63; 1.21]; 0.414
Side effects					
AEs (supplementary information)	142	ND 136 (95.8)	135	ND 130 (96.3)	-
SAEs	142	ND 52 (36.6)	135	ND 46 (34.1)	0.82 [0.55; 1.23] 0.340[c]
Severe AEs (CTCAE grade ≥ 3)	142	ND 67 (47.2)	135	ND 76 (56.3)	0.49 [0.35; 0.70] < 0.001
Discontinuation due to AEs	142	12 (8.5)	135	30 (22.2)	RR: 0.38 [0.20; 0.71]; 0.001[d]

(continued)

Table 5: Results of the POPLAR study at the data cut-off 7 April 2017 (continued)

Study	**Atezolizumab**		**Docetaxel**		**Atezolizumab vs. docetaxel**
Outcome category Outcome	**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]**
POPLAR					
Specific adverse events					
Alopecia	142	ND 3 (2.1)	135	ND 52 (38.5)	0.04 [0.01; 0.12] < 0.001
Immune-related AEs				No usable data	
Immune-related SAEs				No usable data	
Immune-related severe AEs (CTCAE grade ≥ 3)				No usable data	
Pneumonia (PT) as SAE				No usable data	
Respiratory, thoracic and mediastinal disorders (SOC) as SAE				No usable data	
Blood and lymphatic system disorders (SOC) severe AE (CTCAE grade ≥ 3)				No usable data	
- including: febrile neutropenia (PT) as severe AE (CTCAE grade ≥ 3)				No usable data	
Gastrointestinal disorders (SOC) as severe AE (CTCAE grade ≥ 3)				No usable data	
Musculoskeletal and connective tissue disorders (SOC) as severe AE (CTCAE grade ≥ 3)				No usable data	

(continued)

Table 5: Results of the POPLAR study at the data cut-off 7 April 2017 (continued)

a: Effect, CI: Cox proportional hazards model, p-value: log-rank test; unless designated otherwise, in each case stratified by PD-L1 status, number of chemotherapeutic regimens (1 vs. 2) and histology (squamous vs. non-squamous).
b: Time to deterioration is operationalized as time to first increase in the respective score by at least 10 points from baseline. To be rated as deterioration, there had to be an increase in score over at least 2 consecutive cycles, or an initial increase was followed by the patient's death within 3 weeks.
c: Effect, CI: Cox proportional hazards model, p-value: log-rank test, each unstratified.
d: Institute's calculation of effect, RR, CI (asymptotic) and p-value (unconditional exact test [CSZ method according to [8]]).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 6: Subgroups (time to event) – results of the POPLAR study at the data cut-off 7 April 2017 for outcomes or characteristics with a relevant effect modification in the OAK study

Study Outcome Characteristic Subgroup	Atezolizumab N	Atezolizumab Median time to event in months [95% CI] Patients with event n (%)	Docetaxel N	Docetaxel Median time to event in months [95% CI] Patients with event n (%)	Atezolizumab vs. docetaxel HR [95% CI]	Atezolizumab vs. docetaxel p-value
POPLAR						
Mortality						
Overall survival						
PD-L1 status						
TC3 or IC3	24	19.9 [9.8; 41.6] 16 (66.7)	23	11.1 [6.7; 14.4] 19 (82.6)	0.52 [0.26; 1.03]	0.057
TC0/1/2 and IC0/1/2	120	11.1 [9.0; 14.8] 99 (82.5)	120	9.4 [8.3; 11.9] 100 (83.3)	0.80 [0.60; 1.06]	0.113
Morbidity						
Symptoms (EORTC QLQ-C30 symptom scales) – time to deterioration						
Diarrhoea						
PD-L1 status						
TC3 or IC3	23	25.6 [3.7; NC] 11 (47.8)	22	3.6 [2.2; 4.1] 10 (45.5)	0.36 [0.13; 1.03]	0.049
TC0/1/2 and IC0/1/2	116	11.8 [4.1; NC] 43 (37.1)	108	4.7 [3.1; NC] 40 (37.0)	0.75 [0.48; 1.17]	0.200
Appetite loss						
PD-L1 status						
TC3 or IC3	23	8.0 [2.8; NC] 11 (47.8)	22	3.8 [0.9; NC] 12 (54.5)	0.55 [0.23; 1.31]	0.174
TC0/1/2 and IC0/1/2	115	2.1 [1.4; 3.3] 67 (58.3)	110	3.7 [2.2; 15.3] 46 (41.8)	1.39 [0.95; 2.05]	0.090
Side effects						
SAEs						
PD-L1 status						
TC3 or IC3	22	ND 5 (22.7)	23	ND 10 (43.5)	0.31 [0.10; 0.94]	0.030
TC0/1/2 and IC0/1/2	120	ND 47 (39.2)	112	ND 36 (32.1)	0.98 [0.63; 1.53]	0.934

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; IC: immune cells; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; QLQ-C30: Quality of Life Questionnaire-Core 30; TC: tumour cells