IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Atezolizumab (non-small cell lung cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Atezolizumab (nicht kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 December 2017). 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
BSC	best supportive care
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IC	immune cells
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
PT	Preferred Term
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
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TC	tumour cells

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 29 September 2017.

Research question

The aim of the present report was to assess the added benefit of atezolizumab in comparison with the appropriate comparator therapy (ACT) in adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with epidermal growth factor receptor (EGFR) activating mutations or anaplastic lymphoma kinase (ALK)-positive tumour mutations should also have received targeted therapy before receiving atezolizumab.

For the benefit assessment of atezolizumab, the research questions presented in Table 2 resulted from the ACTs specified by the G-BA.

Table 2: Research questions of the benefit assessment of atezolizumab

Research question	**Subindication**[a]	**ACT**[b]
1	Adult patients with locally advanced or metastatic NSCLC after prior chemotherapy for whom treatment with docetaxel, pemetrexed or nivolumab is indicated[c]	**Docetaxel**, pemetrexed[d] or nivolumab
2	Adult patients with locally advanced or metastatic NSCLC after prior chemotherapy for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated[c]	Best supportive care[e]

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: Patients with activating EGFR mutations or ALK translocations should also have received targeted therapy before receiving atezolizumab.
d: Except in mainly squamous histology.
e: 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; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

The company followed the G-BA's specification of the ACT. For research question 1, it chose docetaxel from the options presented in Table 2.

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

Results on research question 1: patients for whom treatment with docetaxel, pemetrexed or nivolumab is indicated

Study pool

The study pool for the benefit assessment of atezolizumab in comparison with the ACT consisted of the RCTs OAK and POPLAR and deviated from the study pool of the company. The company had also identified the POPLAR study, but did not include this study in the study pool.

Both studies (OAK and POPLAR) were open-label RCTs on the comparison of atezolizumab versus docetaxel. The company excluded the POPLAR study because of unapproved formulations of atezolizumab. Dosage and use in the POPLAR study were in compliance with the recommendations of the Summary of Product Characteristics (SPC), however, and the formulations of both studies did not differ in the type of their components. The study pool of the company was therefore incomplete.

Consequences of the incomplete study pool of the company

The POPLAR study included notably fewer patients than the OAK study considered by the company. It comprised 19% of the patients relevant for research question 1. With the OAK study, the company therefore presented the largest part of the evidence in its dossier.

Module 5 of the dossier contained only incomplete documents for the POPLAR study. In particular, there were no time-adjusted analyses and calculations from meta-analyses for the studies OAK and POPLAR.

Against this background, the assessment of the added benefit in the present report was based on the results of the OAK study, which constituted the notably larger proportion of patients relevant for the research question (81%). If available, results from the POPLAR study were considered in qualitative terms for individual outcomes to be able to assess whether they raise principle doubts about the results from the OAK study.

Characteristics of the studies OAK and POPLAR

The studies OAK and POPLAR were open-label RCTs on the comparison of atezolizumab versus docetaxel. 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 OAK study, a total of 1225 patients were randomly allocated in a ratio of 1:1, 613 of them to the atezolizumab arm and 612 to the docetaxel arm. 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. Administration of atezolizumab and docetaxel was in compliance with the approval in both studies. Primary outcome of the studies OAK and POPLAR was overall survival. Patient-relevant secondary outcomes were symptoms, health-related quality of life, and adverse events (AEs).

The following information refers to the OAK study.

Risk of bias

The risk of bias at study level for the OAK study was rated as low. The risk of bias at outcome level was rated as high for all outcomes except for the outcome "overall survival".

Results

Mortality

The OAK study showed a statistically significant difference in favour of atezolizumab in comparison with docetaxel for the outcome "overall survival". In addition, there was an effect modification by the characteristic "programmed cell death ligand 1 (PD-L1) status" (tumour cells [TC]3 or tumour-infiltrating immune cells [IC]3 versus TC0/1/2 and IC0/1/2) for this outcome. This resulted in an indication of an added benefit of atezolizumab in comparison with docetaxel for patients with high PD-L1 expression (TC3 or IC3). For patients with low PD-L1 expression (TC0/1/2 and IC0/1/2), there was no hint of an added benefit of atezolizumab in comparison with docetaxel; an added benefit is not proven for these patients.

Morbidity

- Symptoms

Symptom outcomes were recorded with the symptom scales of the disease-specific instruments European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and EORTC Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13), but only until the end of treatment (generally due to progression of the disease). The time to deterioration by at least 10 points was considered.

  - Haemoptysis, pain (chest), sore mouth, dysphagia, peripheral neuropathy, alopecia

    A statistically significant difference in favour of atezolizumab in comparison with docetaxel was shown for each of the following outcomes: haemoptysis, pain (chest), sore mouth, dysphagia, peripheral neuropathy, and alopecia.

    The certainty of the result of the outcome "alopecia" was upgraded to an indication due to the size of the effect and the number of observed events for this outcome. This

resulted in an indication of an added benefit of atezolizumab in comparison with docetaxel for this outcome and in a hint of an added benefit of atezolizumab for each of the remaining 5 outcomes.

- Diarrhoea, appetite loss

  Statistically significant differences in favour of atezolizumab in comparison with docetaxel were shown for the outcomes "diarrhoea" and "appetite loss". There was an effect modification by the characteristic "PD-L1 status" for both outcomes.

  For the outcome "diarrhoea", a statistically significant difference in favour of atezolizumab was shown both for patients with high PD-L1 expression (TC3 or IC3) and for patients with lower PD-L1 expression (TC0/1/2 and IC0/1/2). This resulted in a hint of an added benefit of atezolizumab in comparison with docetaxel for these patients. The effect modification is reflected in differences in the extent of the added benefit for this outcome.

  For the outcome "appetite loss", a statistically significant difference in favour of atezolizumab was shown for patients with high PD-L1 expression (TC3 or IC3). This resulted in a hint of an added benefit of atezolizumab in comparison with docetaxel for these patients. In contrast, there was no statistically significant difference between the treatment groups for patients with lower PD-L1 expression (TC0/1/2 and IC0/1/2). For patients with lower PD-L1 expression (TC0/1/2 and IC0/1/2), this resulted in no hint of an added benefit of atezolizumab in comparison with docetaxel; hence an added benefit is not proven.

- Nausea and vomiting

  A statistically significant difference in favour of atezolizumab in comparison with docetaxel was shown for the outcome "nausea and vomiting". The extent of the added benefit for this outcome from the category "non-serious/non-severe symptoms/late complications" was no more than marginal. Hence there was no hint of an added benefit of atezolizumab in comparison with docetaxel; an added benefit is therefore not proven.

- Further symptom outcomes

  No statistically significant differences between the treatment groups were shown for any further symptom outcomes. Hence there was no hint of an added benefit of atezolizumab in comparison with docetaxel for any further symptom outcomes; 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, but only until the end of treatment (plus 30 days, generally due to progression of the disease). The time to deterioration by at least 10 points was considered.

No statistically significant differences between the treatment groups were shown for any of the scales. Hence there was no hint of an added benefit for the outcomes of health-related quality of life; an added benefit is not proven for these outcomes.

Side effects

- Serious adverse events

A statistically significant difference in favour of atezolizumab between the treatment groups was shown for the outcome "serious adverse events (SAEs)".

There was an effect modification by the characteristic "PD-L1 status" for the outcome "SAEs". A statistically significant difference in favour of atezolizumab was shown for patients with high PD-L1 expression (TC3 or IC3). This resulted in a hint of lesser harm of atezolizumab in comparison with docetaxel for these patients. There was no statistically significant difference between the treatment groups for patients with lower PD-L1 expression (TC0/1/2 and IC0/1/2). This resulted in no hint of lesser harm of atezolizumab in comparison with docetaxel for these patients; lesser harm is therefore not proven for patients with lower PD-L1 expression (TC0/1/2 and IC0/1/2).

- Severe adverse events (CTCAE grade ≥ 3), discontinuation due to adverse events

Statistically significant differences in favour of atezolizumab between the treatment groups were shown for each of the outcomes "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)" and "discontinuation due to AEs". This resulted in a hint of lesser harm of atezolizumab in comparison with docetaxel for each of these outcomes.

- Specific adverse events
  - Immune-related severe adverse events (CTCAE grade ≥ 3)

    Statistically significant differences to the disadvantage of atezolizumab in comparison with docetaxel were shown for the outcome "immune-related severe AEs (CTCAE grade ≥ 3)". The certainty of the result of this outcome was upgraded to an indication due to the size of the effect and the number of observed events. This resulted in an indication of greater harm of atezolizumab in comparison with docetaxel.
  - Further specific adverse events

    Statistically significant differences in favour of atezolizumab in comparison with docetaxel were shown for each of the following further specific AE outcomes chosen: alopecia, pneumonia, blood and lymphatic system disorders, febrile neutropenia, and gastrointestinal disorders. The certainty of the results of the AE outcomes "alopecia" and "blood and lymphatic system disorders" (including febrile neutropenia recorded in this category) was upgraded to an indication due to the size of the effect and the number of observed events for these outcomes. This resulted in an indication of lesser

harm of atezolizumab in comparison with docetaxel for these outcomes and in a hint of lesser harm of atezolizumab for each of the remaining 2 outcomes.

There were statistically significant differences to the disadvantage of atezolizumab in comparison with docetaxel for each of the specific AE outcomes "respiratory, thoracic and mediastinal disorders" and "musculoskeletal and connective tissue disorders". This resulted in a hint of greater harm of atezolizumab in comparison with docetaxel for each of these outcomes.

Estimation of the influence of the POPLAR study on the result of the benefit assessment

It can be excluded for the outcome "overall survival" that the advantage of atezolizumab in patients with high PD-L1 status (TC3 or IC3) found in the OAK study is challenged by the data from the POPLAR study. Instead, the data confirmed the effects and their extent observed in the OAK study.

The available naive frequencies on SAEs, severe AEs, and discontinuations due to AEs showed no signs that would raise general doubts about the effects found; the size of the effects was unclear due to a lack of time-adjusted analyses, however.

Results on research question 2: patients for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated

For research question 2, no data were available for the benefit assessment of atezolizumab in comparison with the ACT.

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

Research question 1: patients for whom treatment with docetaxel, pemetrexed or nivolumab is indicated

The results showed an effect modification by the patients' PD-L1 status for several outcomes of the categories of mortality, morbidity, and side effects. Hereinafter, the overall conclusion on the added benefit is therefore derived separately for each PD-L1 status.

Patients with high PD-L1 status (TC3 or IC3)

In the overall consideration, there were mostly positive effects of atezolizumab in comparison with docetaxel for patients with high PD-L1 status (TC3 or IC3).

[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].

On the positive side, there was an indication of major added benefit for the outcome "overall survival". In addition, there were hints or an indication of a minor or considerable added benefit for several symptom outcomes.

Positive effects outweighed negative effects also regarding side effects. Among other things, there was overall a hint of lesser harm of major extent for the outcomes "SAEs" and "severe AEs (CTCAE grade ≥ 3)". Regarding specific AEs, there were both positive effects (including febrile neutropenia) and negative effects (including immune-related severe AEs) of partly major extent. In the overall consideration, the negative effects outweighed neither the added benefit in general nor the extent of the added benefit because of the high number and the size of the positive effects. Hence an indication of a major added benefit of atezolizumab can be derived from the results of the OAK study.

Patients with low PD-L1 status (TC0/1/2 or IC0/1/2)

In the overall consideration, there were positive and negative effects of atezolizumab in comparison with docetaxel also for patients with low PD-L1 status (TC0/1/2 and IC0/1/2).

Mostly positive effects were shown also for the patient group with low PD-L1 status. However, there was no evidence of an advantage in the outcome "overall survival". Besides, the effects in the categories of symptoms and AEs were either not visible (e.g. in SAEs) or less pronounced (e.g. diarrhoea). In view of the missing data of the POPLAR study, this did not raise general doubts about the added benefit, but the added benefit for the patient group with low PD-L1 status is non-quantifiable in the present data situation.

Hence overall, an indication of a non-quantifiable added benefit of atezolizumab in comparison with the ACT docetaxel was derived for patients with low PD-L1 status (TC0/1/2 and IC0/1/2).

Research question 2: patients for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated

No data were available for the assessment of the added benefit of atezolizumab in comparison with best supportive care (BSC) for patients with locally advanced or metastatic NSCLC after prior chemotherapy for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated. Hence there was no hint of an added benefit of atezolizumab in comparison with the BSC for these patients; an added benefit is therefore not proven.

Table 3 presents a summary of probability and extent of the added benefit of atezolizumab.

Table 3: Atezolizumab – probability and extent of added benefit

Research question[a]	**Subindication**[a]	**ACT**[b]	**Probability and extent of added benefit**
1	Adult patients with locally advanced or metastatic NSCLC after prior chemotherapy for whom treatment with docetaxel, pemetrexed or nivolumab is indicated[c]	**Docetaxel**, pemetrexed[d] 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[c]	Best supportive care[e]	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: Patients with activating EGFR mutations or ALK translocations should also have received targeted therapy before receiving atezolizumab.
d: Except in mainly squamous histology.
e: 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 approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of atezolizumab in comparison with the ACT in adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving atezolizumab.

For the benefit assessment of atezolizumab, the research questions presented in Table 4 resulted from the ACTs specified by the G-BA.

Table 4: Research questions of the benefit assessment of atezolizumab

Research question	Subindication[a]	ACT[b]
1	Adult patients with locally advanced or metastatic NSCLC after prior chemotherapy for whom treatment with docetaxel, pemetrexed or nivolumab is indicated[c]	**Docetaxel**, pemetrexed[d] or nivolumab
2	Adult patients with locally advanced or metastatic NSCLC after prior chemotherapy for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated[c]	Best supportive care[e]

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: Patients with activating EGFR mutations or ALK translocations should also have received targeted therapy before receiving atezolizumab.
d: Except in mainly squamous histology.
e: 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; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

The company followed the G-BA's specification of the ACT. For research question 1, it chose docetaxel from the options presented in Table 4.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided 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 Research question 1: patients for whom treatment with docetaxel, pemetrexed or nivolumab is indicated

2.3.1 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: 13 July 2017)
- bibliographical literature search on atezolizumab (last search on 13 July 2017)
- search in trial registries for studies on atezolizumab (last search on 13 July 2017)

To check the completeness of the study pool:

- search in trial registries for studies on atezolizumab (last search on 4 October 2017)

Besides the OAK study considered by the company, the check also identified the relevant POPLAR study. The company had cited this study in its study list, but had excluded it from the assessment.

2.3.1.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: atezolizumab vs. docetaxel

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
GO28915 (OAK[b])	Yes	Yes	No
GO28753 (POPLAR[b])	Yes	Yes	No

a: Study for which the company was sponsor.
b: In the following tables, the study is referred to with this abbreviated form.
RCT: randomized controlled trial; vs.: versus

The study pool of the present assessment of the added benefit of atezolizumab deviated from that of the company, which only included the OAK study. The company did not include the POPLAR study in its study pool and did not use it for the derivation of the added benefit.

Both studies (OAK and POPLAR) were open-label RCTs on the comparison of atezolizumab versus docetaxel.

According to the company, the formulation of atezolizumab used in the POPLAR study did not concur with the approved formulation. The company provided no further information on the differences of the formulation and on the reasons why it considered these to be so relevant that the study could not be used. The company's assessment that the study was not relevant was not followed.

Formulations of atezolizumab in the studies OAK and POPLAR

The approval-compliant dose of 1200 mg atezolizumab as infusion every 3 weeks was used in both studies (OAK and POPLAR). It can be inferred from both the European Public Assessment Report (EPAR) and the study documents that different formulations were used in the 2 atezolizumab studies [3]. Both formulations contained the same components: atezolizumab, histidine acetate, sucrose, and polysorbate 20. They differed in the concentration of these substances in the original solutions. A solution for intravenous infusion is prepared from both formulations before the drug is used. The initial dose of this preparation was delivered over 60 minutes. If the first infusion was tolerated, subsequent infusions were delivered over 30 minutes. This concurs with the information provided in the SPC on atezolizumab [4]. The documents did not provide information how exactly the solution for infusion was prepared for the POPLAR study. Eventually, dosage and use in the POPLAR study were in compliance with the recommendations of the SPC, however, and the formulation did not differ in the type of its components. Due to the application form as parenteral solution, also no potential differences in bioavailability due to differences in resorption can be expected. The European Medicines Agency (EMA) also rated the formulations as comparable [3]. Against this background, it was inadequate to exclude the POPLAR study. The study pool of the company was therefore incomplete.

Consequences of the incomplete study pool of the company

The POPLAR study included notably fewer patients than the OAK study considered by the company. It comprised 19% of the patients relevant for research question 1. With the OAK study, the company therefore presented the largest part of the evidence in its dossier.

Module 5 of the dossier contained only incomplete documents for the POPLAR study. In particular, there were no time-adjusted analyses and calculations from meta-analyses for the studies OAK and POPLAR.

Against this background, the assessment of the added benefit in the present report was based on the results of the OAK study, which constituted the notably larger proportion of patients relevant for the research question (81%). If available, results from the POPLAR study were considered in qualitative terms for individual outcomes to be able to assess whether they raise principle doubts about the results from the OAK study.

Section 2.3.5 contains a reference list for the studies included.

2.3.1.2 Study characteristics

Study design

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

Table 6: Characteristics of the studies included – RCT, direct comparison: atezolizumab vs. docetaxel

Study	Study design	Population	Interventions (numbers of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
OAK	RCT, open-label, parallel	Adults (≥ 18 years) with locally advanced or metastatic NSCLC, ECOG PS 0 or 1, and progression during or after prior platinum-based chemotherapy for advanced disease[c]	Primary analysis population[b]: atezolizumab (N = 425) docetaxel (N = 425) Secondary analysis population: atezolizumab (N = 613) docetaxel (N = 612)	Screening: 28 days Treatment: until progression, withdrawal of consent, unacceptable toxicity, or until death Follow-up observation: every 2–3 months until death, discontinuation of participation in the study, or end of study	194 centres in America, Europe, Asia 3/2014–ongoing **First data cut-off:** 7 July 2016 **Second data cut-off:** 23 January 2017	Primary: overall survival Secondary: symptoms, health-related quality of life, AEs
POPLAR	RCT, open-label, parallel	Adults (≥ 18 years) with locally advanced or metastatic NSCLC, ECOG PS 0 or 1, and progression during or after platinum-based chemotherapy for advanced disease[c]	Atezolizumab (N = 144) docetaxel (N = 143)	Screening: 28 days Treatment: until progression, withdrawal of consent, unacceptable toxicity, or until death Follow-up observation: every 3 months until death, discontinuation of participation in the study, or end of study	61 centres in North America, Europe, Asia 8/2013–ongoing **Data cut-off (primary analysis):** 8 May 2015 **Further data cut-off:** 1 December 2015	Primary: overall survival Secondary: symptoms, health-related quality of life, AEs

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for this benefit assessment.
b: The population is not relevant for the assessment and is not shown in the following tables.
c: Includes no more than 2 cytotoxic chemotherapies; combined treatment with chemotherapy and radiation was counted as one pretreatment.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; N: number of randomized patients; NSCLC: non-small cell lung cancer; RCT: randomized controlled trial; vs.: versus

Table 7: characteristics of the interventions – RCT, direct comparison: atezolizumab vs. docetaxel

Study	Atezolizumab	Docetaxel
OAK	1200 mg atezolizumab intravenously in cycles of 21 (±3) days	Starting dose of 75 mg/m^2 docetaxel intravenously in cycles of 21 days Premedication: corticosteroids 16 mg/day (8 mg twice daily) for 3 days, from 1 day before start of treatment
	Dose adjustments and interruptions: ▪ Dose reduction not allowed ▪ Treatment interruption due to AEs ≤ 105 days allowed ▪ Treatment interruption > 105 days due to AEs: ▫ treatment interruption by investigator or ▫ treatment continuation after consultation with monitor ▫ in patients under tapering steroid therapy until discontinuation of steroids or steroid reduction to ≤ 10 mg/day if approved by investigator and monitor	Dose adjustments: ▪ treatment interruption and continuation with 55 mg/m² docetaxel in case of febrile neutropenia (neutrophil cell count < 500/mm³ for > 1 week), severe skin reactions or other non-haematological grade 3 or 4 toxicities after starting dose of 75 mg/m^2 docetaxel ▪ treatment discontinuation in case of grade > 3 peripheral neuropathy ▪ dosage modification in compliance with local SPC
	Pretreatment: Pretreatment: ▪ systemic cytotoxic and/or platinum-based chemotherapy until ≥ 21 days before randomization; TKIs until ≥ 7 days before cycle 1, day 1 ▪ patients with activating EGFR tumour mutations: EGFR tyrosine kinase inhibitor (e.g. erlotinib or gefitinib) ▪ patients with ALK tumour mutations: ALK inhibitor (e.g. crizotinib) Non-permitted pretreatment: ▪ oral or intravenous antibiotics > 2 weeks before randomization ▪ major surgical interventions > 4 weeks before randomization or during the study ▪ docetaxel ▪ CD137 agonists, anti-CTLA4, anti-PD-1 or anti-PD-L1 antibodies or targeted drugs ▪ systemic corticosteroids or other immunosuppressants (e.g. prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, anti-TNF agents) until ≥ 2 weeks before randomization ▪ live vaccines > 4 weeks before randomization or during the study ▪ systemic immunostimulatory agents (e.g. interferons or interleukin 2) > 4 weeks or 5 times the half-life before randomization	

(continued)

Table 7: characteristics of the interventions – RCT, direct comparison: atezolizumab vs. docetaxel (continued)

Study	Atezolizumab	Docetaxel
	Concomitant treatment: Concomitant treatment permitted: ▪ inhaled corticosteroids and mineral corticosteroids (e.g. fludrocortisone) ▪ prophylactic administration of antibiotics (e.g. for prevention of urinary tract infection, chronic obstructive pulmonary disease) ▪ oral contraceptives, hormone replacement therapy, prophylactic or therapeutic anticoagulants (e.g. low molecular weight heparin or warfarin) at a stable dose ▪ bisphosphonates for prevention of skeletal-related events ▪ analgesics at a stable dosage at the start of the study ▪ megestrol to stimulate appetite ▪ antipyretics (preferably ibuprofen), diphenhydramine and/or cimetidine, or other H2 receptor antagonists ▪ after cycle 1, day 14 radiotherapy for alleviation of pain Docetaxel arm: ▪ granulocyte-stimulating medications ▪ antiemetics, antiallergics if approved by the investigator Atezolizumab arm: ▪ ≥ cycle 2 systemic corticosteroids, TNFα inhibitors; epinephrine, antihistamines for the treatment of AEs Non-permitted concomitant treatment: Docetaxel: ▪ CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, or voriconazole) Atezolizumab: ▪ active immunization with live vaccines during the study ▪ herbal drugs ▪ immunomodulatory drugs (until 10 weeks after end of study) and immunosuppressants ▪ RANKL inhibitor (denosumab)	

(continued)

Table 7: characteristics of the interventions – RCT, direct comparison: atezolizumab vs. docetaxel (continued)

Study	Atezolizumab	Docetaxel
POPLAR	1200 mg atezolizumab intravenously in cycles of 21 (±2) days	Starting dose of 75 mg/m^2 docetaxel intravenously in cycles of 21 days Premedication: corticosteroids 16 mg/day (8 mg twice daily) for 3 days, from 1 day before start of treatment
	Dose adjustments: ▪ dose reduction not allowed ▪ treatment interruption < 105 days allowed ▪ interruption of medication ≥ 105 possible after consultation with Medical Monitor	Dose adjustments: ▪ treatment interruption and continuation with 55 mg/m² docetaxel in case of febrile neutropenia (neutrophil cell count < 500/mm³ for > 1 week), severe skin reactions or other non-haematological grade 3 or 4 toxicities after starting dose of 75 mg/m^2 docetaxel ▪ discontinuation of treatment in case of grade 4 toxicity[b] or repeated grade 3 toxicity after dose reduction Dosage modification in compliance with local SPC
	Pretreatment: Pretreatment: ▪ systemic cytotoxic and/or platinum-based chemotherapy until ≥ 21 days before randomization; vinorelbine ≥ 14 days or vinca alkaloids or gemcitabine ≤ 4 weeks or 5 times the half-life before randomization ▪ patients with activating EGFR tumour mutations: EGFR tyrosine kinase inhibitor (e.g. erlotinib or gefitinib) if treatment standard ▪ patients with ALK tumour mutations: ALK inhibitor (e.g. crizotinib) Non-permitted pretreatment: ▪ oral or intravenous antibiotics > 2 weeks before randomization ▪ major surgical interventions > 4 weeks before randomization or during the study ▪ live vaccines > 4 weeks before randomization or during the study ▪ Docetaxel ▪ CD137 agonists, anti-CTLA4, anti-PD-1 or anti-PD-L1 antibodies or targeted drugs ▪ systemic immunostimulatory agents (e.g. interferons or interleukin 2) > 4 weeks or 5 times the half-life before randomization ▪ systemic immunosuppressants (e.g. prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, anti-TNF agents) until ≥ 2 weeks before randomization	

(continued)

Table 7: characteristics of the interventions – RCT, direct comparison: atezolizumab vs. docetaxel (continued)

	Concomitant treatment: Concomitant treatment permitted: ▪ analgesics at a stable dosage at the start of the study ▪ antipyretics (preferably ibuprofen), diphenhydramine and/or cimetidine, or other H2 receptor antagonists ▪ megestrol to stimulate appetite ▪ oral contraceptives, hormone replacement therapy, prophylactic or therapeutic anticoagulants (e.g. low molecular weight heparin or warfarin) at a stable dose ▪ after cycle 1, day 14 radiotherapy for alleviation of pain ▪ bisphosphonates for prevention of skeletal-related events Docetaxel: ▪ granulocyte-stimulating medications ▪ antiemetics, antiallergics if approved by the investigator Atezolizumab: ▪ ≥ cycle 2 systemic corticosteroids, TNFα inhibitors; epinephrine, antihistamines for the treatment of AEs Non-permitted concomitant treatment: Docetaxel: ▪ CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, or voriconazole) Atezolizumab: ▪ active immunization with live vaccines during the study ▪ herbal drugs ▪ immunomodulatory drugs (until 10 weeks after end of study) and immunosuppressants ▪ RANKL inhibitor (denosumab)
AE: adverse event; ALK: anaplastic lymphoma kinase; CD: cluster of differentiation; CTLA: cytotoxic T-lymphocyte-associated antigen; CYP: cytochrome; EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RANKL: receptor activator of nuclear factor-κB ligand; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; TNF: tumour necrosis factor; TKI: tyrosine kinase inhibitor; vs.: versus	

Study OAK

The OAK study was a randomized, open-label, controlled phase 3 study on the comparison of atezolizumab with docetaxel. The study 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. Patients with EGFR mutation of the tumour additionally had to have progressed after treatment with an EGFR tyrosine kinase inhibitor (e.g. erlotinib, gefitinib); patients diagnosed with ALK-positive tumour had to have progressed after treatment with crizotinib (or another ALK inhibitor). Another inclusion criterion was an ECOG PS of 0 or 1, and hence good general condition of the participants.

850 patients (primary analysis population) were initially included in the study; after protocol adjustment, a total of 1225 patients (secondary analysis population) were then randomly

allocated in a ratio of 1:1, 613 of them to the atezolizumab arm and 612 to the docetaxel arm. Randomization was stratified by PD-L1 status (PD-L1 expression on tumour-infiltrating immune cells [IC0, IC1, IC2, and IC3], number of prior lines of chemotherapy [1 versus 2], and histology [squamous versus non-squamous]). PD-L1 status on study inclusion was determined in a central laboratory using Roche's VENTANA PD-L1 (SP142) IHC assay.

Patients in the atezolizumab arm received 1200 mg atezolizumab as infusion every 3 weeks. Application of the experimental intervention corresponded to the requirements of the SPC [4]. Patients in the comparator arm received intravenous docetaxel 75 mg/m^2 body surface area every 3 weeks. The application also corresponded to the requirements of the SPC [3].

Overall survival was the primary outcome of the OAK study. Patient-relevant secondary outcomes were symptoms, health-related quality of life, and AEs.

Treatment with the study medication was continued until a criterion for discontinuation occurred, e.g. unacceptable toxicity or disease progression (see Table 6). After discontinuation of the study medication (e.g. due to disease progression), the patients in both treatment arms could be treated with subsequent therapies. In the secondary analysis population, 40.9% of the patients in the atezolizumab arm and 26.1% of the patients in the docetaxel arm received subsequent chemotherapy after the first disease progression. Subsequent immunotherapy (in particular with nivolumab or pembrolizumab) was given to 5.4% of the patients in the atezolizumab arm and to 20.6% of the patients in the docetaxel arm. With Amendment 6 to the study protocol (7 December 2016), patients in the secondary analysis population in the docetaxel were allowed to cross over to the atezolizumab arm. No such treatment switching occurred until the data cut-off on 23 January 2017, however.

Data cut-offs and analyses

The OAK study is still ongoing. It was originally planned with a sample size of 850 patients (primary analysis population). The company adapted the sample size planning during the course of the study: based on new findings (including findings from the POPLAR study), the study was resized from initially 850 to between 1100 and 1300 patients to power the study for the subgroup of patients with high PD-L1 expression of the tumour or immune cells (TC3 or IC3). Hence results on 2 different analysis populations and also on 2 different data cut-offs (7 July 2016 [primary data cut-off] and 23 January 2017 [secondary data cut-off]) were available for the present study. Deviating from the company, the present benefit assessment for all outcomes was conducted based on the secondary analysis population (N = 1225) and on the secondary analysis cut-off from 23 January 2017 (see Section 2.6.2.4.3 of the full dossier assessment). Unless designated otherwise, the following information therefore refers to the secondary analysis population.

Study POPLAR

The POPLAR study was a randomized, open-label, controlled phase 2 study, which also compared atezolizumab with docetaxel. The inclusion criteria largely concurred with those of the OAK study.

In the study, 287 patients were randomly allocated in a ratio of 1:1, 144 patients to the atezolizumab arm and 143 patients to the docetaxel arm. Patients in the atezolizumab arm received 1200 mg atezolizumab as infusion every 3 weeks. Patients in the comparator arm received intravenous docetaxel 75 mg/m^2 body surface area every 3 weeks. Hence the application of atezolizumab docetaxel concurred with the requirements of the respective SPCs.

Overall survival was the primary outcome of the POPLAR study. Patient-relevant secondary outcomes were symptoms, health-related quality of life, and AEs.

As described above, not all the necessary information was available for the POPLAR study. The following sections therefore refer primarily to the OAK study.

Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: atezolizumab vs. docetaxel

Study **Outcome category** **Outcome**	**Planned follow-up**
OAK	
Mortality	
Overall survival	After disease progression and discontinuation of the study treatment, every 2 to 3 months until death, loss to follow-up or end of study
Morbidity	
Symptoms	
EORTC QLQ-C30 symptom scales EORTC QLQ-LC13	On day 1 of each cycle[a] and within 30 days after the last dose of the study medication
Health-related quality of life	
EORTC QLQ-C30 functional scales	On day 1 of each cycle[a] and within 30 days after the last dose of the study medication
Side effects	
All outcomes in the category "side effects"	Up to 30 days after the last dose of the study medication or initiation of another anticancer therapy
a: One cycle is 21 days. EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire Core30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer-13; RCT: randomized controlled trial; vs.: versus	

The observation periods for the outcomes "morbidity", "health-related quality of life" and "side effects" were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Characteristics of the study population

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

Table 9: Characteristics of the study population – RCT, direct comparison: atezolizumab vs. docetaxel

Study **Characteristics** **Category**	**Atezolizumab**	**Docetaxel**
OAK	N[a] = 613	N[a] = 612
Age [years], mean (SD)	62.7 (9.8)	62.9 (9.2)
Sex [F/M], %	38.2/61.8	38.1/61.9
Ethnicity, n (%)		
Asian	124 (20.2)	125 (20.4)
White	438 (71.5)	432 (70.6)
Other[b]	51 (8.3)	55 (9.0)
Region, n (%)		
North America	160 (26.1)	185 (30.2)
Europe[c]	317 (51.7)	296 (48.4)
Other[d]	136 (22.2)[e]	131 (21.5)[e]
Smoking status, n (%)		
Never-smoker	112 (18.3)	96 (15.7)
Smoker (current or former)	501 (81.7)	516 (84.3)
ECOG Performance Status, n (%)		
0	221 (36.1)	234 (38.2)
1	392 (63.9)	378 (61.8)
Histology, n (%)		
Squamous	161 (26.3)	160 (26.1)
Non-squamous	452 (73.7)	452 (73.9)
Prior lines of therapy, n (%)		
1	464 (75.7)	465 (76.0)
2	149 (24.3)	147 (24.0)
Current disease status, n (%)		
Locally advanced	38 (6.2)	32 (5.2)
Metastatic disease	575 (93.8)	580 (94.8)
Number of metastases at start of study, mean (SD)	2.92 (1.45)	2.94 (1.31)
Liver metastases at start of study, n (%)	126 (20.6)	125 (20.4)
Bone metastases at start of study, n (%)	193 (31.5)	189 (30.9)
Brain metastases at start of study, n (%)	52 (8.5)	66 (10.8)
EGFR mutation status, n (%)		
Positive	60 (9.8)	53 (8.7)
Negative	455 (74.2)	464 (75.8)
Unknown	98 (16.0)	95 (15.5)

(continued)

Table 9: Characteristics of the study population – RCT, direct comparison: atezolizumab vs. docetaxel (continued)

Study Characteristics Category	Atezolizumab	Docetaxel
Study OAK	N[a] = 613	N[a] = 612
ALK translocation status, n (%)		
Positive	4 (0.7)	1 (0.2)
Negative	315 (51.4)	289 (47.2)
Unknown	294 (48.0)	322 (52.6)
PD-L1 status[f], n (%)		
TC3 or IC3	88 (14.4)	85 (13.9)
TC0/1/2 and IC0/1/2	517 (84.3)	523 (85.5)
Unknown	8 (1.3)	4 (0.7)
Treatment discontinuation[e], n (%)	ND	ND
Study discontinuation[g], 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: Contains the categories Asia, Australia and Oceania, as well as South America.
e: Data cut-off from 7 July 2016, treatment discontinuations in the atezolizumab arm: 524 (85.5%), docetaxel arm: 577 (94.3%).
f: TC3: ≥ 50% TC; IC3: ≥ 10% IC; TC0/1/2: < 50% TC; IC0/1/2: < 10% IC.
g: Data cut-off from 7 July 2016, study discontinuations (including deaths, discontinuation by patient, lost to follow-up): atezolizumab arm 422 (68.8%), docetaxel arm 473 (77.3%). Percentages: Institute's calculation.
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; RCT: randomized controlled trial; SD: standard deviation; TC: tumour cells; vs.: versus

Overall, the patient characteristics between the arms of the OAK study were balanced. The mean age of the patients was about 63 years; most of them were male (62%), and about half of the patients were of European origin. Approximately 76% of the patients had received one prior cytotoxic chemotherapy at study inclusion; 24% had received 2 prior therapies. Approximately 14% of the patients had a high PD-L1 status (TC3 or IC3) at study inclusion.

No data on treatment discontinuation and study discontinuation were available for the data cut-off from 23 January 2017 used. However, the majority of the patients had already discontinued treatment at the previous data cut-off (7 July 2016) (85.5% in the atezolizumab arm, which were fewer patients than in the comparator arm with 94.3%).

Course of the study

Table 10 shows the mean and median treatment duration of the patients in the OAK study.

Table 10: Information on the course of the study – RCT, direct comparison: atezolizumab vs. docetaxel

Study **Duration of the study phase** **Outcome category**	**Atezolizumab**	**Docetaxel**
OAK	N = 609[a]	N = 578[a]
Treatment duration [months]		
Median [min; max]	3.4 [0; 32]	2.1 [0; 30]
Mean (SD)	6.9 (8.3)	3.0 (3.4)
Observation period [months]		
Overall survival	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND	ND

a: Data of the second data cut-off on 23 January 2017.

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

The median treatment duration in the OAK study was notably longer in the atezolizumab arm (3.4 months) than in the docetaxel arm (2.1 months). The difference in treatment durations was caused by differences in the rates of treatment discontinuation due to disease progression and AEs.

The dossier contained no information on observation periods of individual outcomes. It can be assumed, however, that the differences in treatment and observation duration were similar because the outcomes on morbidity, health-related quality of life, and side effects were each recorded for up to 30 days after the last administration of the study medication.

Risk of bias at study level

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: atezolizumab vs. docetaxel

Study	**Adequate random sequence generation**	**Allocation concealment**	**Blinding**		**Reporting independent of the results**	**No additional aspects**	**Risk of bias at study level**
			Patient	**Treating staff**			
OAK	Yes	Yes	No	No	Yes	Yes	Low

RCT: randomized controlled trial; vs.: versus

The risk of bias at study level for the OAK study was rated as low. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described with the outcome-specific risk of bias in Section 2.6.2.4.2 of the full dossier assessment.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the symptom scales of the instruments EORTC QLQ-C30 and EORTC QLQ-LC13
- 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)
  - immune-related AEs
  - 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 2.6.2.4.3 of the full dossier assessment).

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

Table 12: Matrix of outcomes – RCT, direct comparison: atezolizumab vs. docetaxel

Study	Outcomes										
	Overall survival	**Symptoms (EORTC QLQ-C30 and QLQ-LC13)**	**Health-related quality of life (EORTC QLQ-C30)**	**SAEs**	**Discontinuation due to AEs**	**Severe AEs (CTCAE grade ≥ 3)**	**Immune-related AEs**	**Immune-related SAEs**	**Immune-related severe AEs (CTCAE grade ≥ 3)**	**Further specific AEs (alopecia)[a]**	**Further specific AEs[b]**
OAK	Yes	Yes	Yes	Yes	Yes	Yes	No[c]	No[c]	Yes[d]	Yes	Yes

a: The following event is considered (MedDRA coding): "alopecia" (PT in AE).
b: The following events are considered (MedDRA coding): "pneumonia" (PT in SAE), "respiratory, thoracic and mediastinal disorders" (SOC in SAE), "blood and lymphatic system disorders" (SOC in CTCAE grade ≥ 3), "febrile neutropenia" (PT in CTCAE grade ≥ 3), "gastrointestinal disorders" (SOC in CTCAE grade ≥ 3), "musculoskeletal and connective tissue disorders" (SOC in CTCAE grade ≥ 3).
c: No usable data available; for reasons, see Section 2.6.2.4.3 of the full dossier assessment.
d: Results from a different data cut-off (7 July 2016).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; 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; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

2.3.2.2 Risk of bias

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

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: atezolizumab vs. docetaxel

Study	Study level	Outcomes										
		Overall survival	Symptoms (EORTC QLQ-C30 and QLQ-LC13)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Immune-related AEs	Immune-related SAEs	Immune-related severe AEs (CTCAE grade ≥ 3)	Further specific AEs (alopecia)[a]	Further specific AEs[b]
OAK	L	L	H[c, d]	H[c, d]	H[d]	H[e]	H[d]	–[f]	–[f]	H[g, h]	H[d, e]	H[e, h]

a: The following event is considered (MedDRA coding): "alopecia" (PT in AE).
b: The following events are considered (MedDRA coding): "pneumonia" (PT in SAE), "respiratory, thoracic and mediastinal disorders" (SOC in SAE), "blood and lymphatic system disorders" (SOC in CTCAE grade ≥ 3), "febrile neutropenia" (PT in CTCAE grade ≥ 3), "gastrointestinal disorders" (SOC in CTCAE grade ≥ 3), "musculoskeletal and connective tissue disorders" (SOC in CTCAE grade ≥ 3).
c: Due to incomplete blinding in subjective recording of outcomes; large proportion of patients not included in the analysis (> 10%) or large difference between the treatment groups (> 5 percentage points); decreasing response to questionnaires in the course of the study.
d: Potentially large difference in potentially informative censorings between the treatment groups.
e: Lack of blinding in subjective recording of outcomes.
f: No usable data available; for reasons, see Section 2.6.2.4.3 of the full dossier assessment.
g: Results from a different data cut-off (7 July 2016).
h: Large difference in median treatment duration (and hence observation period) between the intervention arm (3.4 months) and the control arm (2.1 months).
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; 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; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

The risk of bias for the outcome "overall survival" was rated as low. This concurs with the company's assessment (see Section 2.6.2.4.2 of the full dossier assessment).

The risk of bias for the outcomes on symptoms and quality of life was rated as high due to lack of blinding in subjective recording of outcomes, the large proportion of patients not included in the assessment, and potentially informative censoring (see Section 2.6.2.4.2 of the full dossier assessment). The risk of bias was also rated as high for the outcome "discontinuation due to AEs" due to lack of blinding. The company also rated the risk of bias as high for these outcomes.

The risk of bias was high for the further outcomes on side effects (SAEs, severe CTCAE grade ≥ 3 AEs, and further specific AEs [alopecia]) due to differences in the observation period between the treatment arms. For alopecia, there was the additional lack of blinding in

subjective recording of outcomes (see Section 2.6.2.4.2 of the full dossier assessment). Regarding immune-related side effects, usable data were only available for severe immune-related AEs (CTCAE grade ≥ 3) and only from the first data cut-off (7 July 2016). The risk of bias was high for this outcome and for further specific AEs due to the large difference in median treatment duration (and hence observation period) between the intervention arm and the control arm. Immune-related severe AEs (CTCAE grade ≥ 3), alopecia, and further specific AEs were not considered by the company.

2.3.2.3 Results

Table 14 summarizes the results on the comparison of atezolizumab with docetaxel from the OAK study.

Unless designated otherwise, the analyses for all outcomes were based on the second data cut-off (23 January 2017) of the secondary analysis population (N = 1225) of the OAK study. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations. Kaplan-Meier curves were only available for the second data cut-off and only for AE outcomes and are presented in Appendix A of the full dossier assessment. Results on common AEs are presented in Appendix B of the full dossier assessment.

Table 14: Results – RCT, direct comparison: atezolizumab vs. docetaxel

Study Outcome category Outcome	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]; p-value[a]
OAK					
Mortality					
Overall survival	613	13.3 [11.3; 14.9] 424 (69.2)	612	9.8 [8.8; 11.3] 441 (72.1)	0.80 [0.70; 0.92]; 0.001
Morbidity					
Symptoms (EORTC QLQ-C30 symptom scales) – time to deterioration[b]					
Nausea and vomiting	609	6.9 [5.0; 11.0] 257 (42.2)	576	4.4 [3.5; 6.3] 234 (40.6)	0.83 [0.69; 0.999]; 0.049
Diarrhoea	609	11.6 [9.1; 17.0] 195 (32.0)	574	4.2 [3.7; 4.9] 221 (38.5)	0.59 [0.48; 0.72]; < 0.001
Appetite loss	609	4.4 [3.1; 6.2] 302 (49.6)	576	3.5 [2.5; 3.8] 271 (47.0)	0.81 [0.68; 0.96]; 0.018
Dyspnoea	609	4.6 [3.5; 5.6] 281 (46.1)	576	3.8 [3.1; 4.6] 240 (41.7)	0.93 [0.77; 1.11]; 0.407
Fatigue	609	1.4 [1.4; 1.6] 418 (68.6)	576	1.4 [1.4; 1.6] 378 (65.6)	0.92 [0.80; 1.07]; 0.272
Insomnia	608	4.9 [3.6; 5.6] 282 (46.4)	576	4.7 [4.2; 7.0] 220 (38.2)	1.00 [0.84; 1.21]; 0.959
Pain	609	2.8 [2.3; 3.5] 342 (56.2)	576	2.8 [2.1; 3.1] 305 (53.0)	0.88 [0.75; 1.03]; 0.130
Constipation	609	5.0 [3.6; 7.2] 274 (45.0)	573	4.9 [4.0; 11.1] 216 (37.7)	1.03 [0.86; 1.24]; 0.740

(continued)

Table 14: Results – RCT, direct comparison: atezolizumab vs. docetaxel (continued)

Study Outcome category Outcome	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]; p-value[a]
Symptoms (EORTC QLQ-LC13 symptom scales) – time to deterioration[b]					
Haemoptysis	608	NA 98 (16.1)	576	25.1 [19.0; NC] 98 (17.0)	0.64 [0.48; 0.87]; 0.004
Pain (chest)	608	15.2 [11.0; 21.9] 198 (32.6)	575	6.4 [4.7; 8.6] 191 (33.2)	0.72 [0.59; 0.89]; 0.002
Sore mouth	608	16.6 [12.8; NC] 166 (27.3)	576	4.2 [2.8; 5.3] 237 (41.1)	0.45 [0.37; 0.56]; < 0.001
Dysphagia	608	15.7 [11.0; 24.1] 180 (29.6)	576	8.6 [4.9; NC] 172 (29.9)	0.69 [0.56; 0.86]; < 0.001
Neuropathy peripheral	608	7.0 [6.2; 10.4] 232 (38.2)	576	3.0 [2.8; 3.5] 269 (46.7)	0.57 [0.47; 0.68]; < 0.001
Alopecia	607	NA [28.2; NC] 99 (16.3)	576	0.8 [0.8; 0.8] 444 (77.1)	0.06 [0.05; 0.08]; < 0.001
Dyspnoea	608	1.7 [1.5; 2.2] 382 (62.8)	575	1.9 [1.6; 2.2] 342 (59.5)	0.96 [0.82; 1.11]; 0.570
Cough	608	5.5 [4.4; 7.7] 259 (42.6)	575	6.0 [4.2; 10.8] 188 (32.7)	1.10 [0.90; 1.33]; 0.350
Pain (arm/shoulder)	608	7.2 [5.6; 11.7] 234 (38.5)	576	7.7 [5.2; NC] 179 (31.1)	1.01 [0.83; 1.24]; 0.901
Pain (other)	607	3.8 [3.1; 5.1] 283 (46.6)	571	4.1 [2.9; 4.7] 245 (42.9)	0.91 [0.76; 1.09]; 0.313

(continued)

Table 14: Results – RCT, direct comparison: atezolizumab vs. docetaxel (continued)

Study Outcome category Outcome	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]; p-value[a]
Health-related quality of life					
EORTC QLQ-C30 functional scales – time to deterioration[b]					
Physical functioning	609	2.9 [2.4; 4.0] 321 (52.7)	577	2.9 [2.4; 3.2] 297 (51.5)	0.86 [0.73; 1.02]; 0.080
Emotional functioning	609	6.9 [4.9; 10.6] 258 (42.4)	575	5.1 [4.2; 8.6] 213 (37.0)	0.90 [0.74; 1.09]; 0.267
Cognitive functioning	609	3.5 [2.9; 4.3] 301 (49.4)	575	3.6 [2.9; 4.7] 248 (43.1)	1.01 [0.85; 1.20]; 0.925
Social functioning	608	3.5 [2.8; 4.4] 307 (50.5)	575	2.6 [2.1; 3.0] 287 (49.9)	0.86 [0.73; 1.02]; 0.075
Global health status	609	2.8 [2.2; 3.1] 345 (56.7)	575	2.4 [2.1; 2.9] 296 (51.5)	0.92 [0.78; 1.08]; 0.295
Role functioning	608	2.1 [1.6; 2.6] 367 (60.4)	576	2.1 [1.6; 2.2] 343 (59.5)	0.87 [0.74; 1.01]; 0.068
Side effects					
AEs (supplementary information)	609	ND 574 (94.3)	578	ND 557 (96.4)	–
SAEs	609	ND 195 (32.0)	578	ND 180 (31.1)	0.75 [0.61; 0.92]; 0.007[c]
Severe AEs (CTCAE grade ≥ 3)	609	ND 243 (39.9)	578	ND 322 (55.7)	0.41 [0.34; 0.49]; < 0.001[c]
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[d]**
Discontinuation due to AEs	609	48 (7.9)	578	106 (18.3)	0.43 [0.31; 0.59]; < 0.001

(continued)

Table 14: Results – RCT, direct comparison: atezolizumab vs. docetaxel (continued)

Study Outcome category Outcome	Atezolizumab N	Atezolizumab Patients with event n (%)	Docetaxel N	Docetaxel Patients with event n (%)	Atezolizumab vs. docetaxel RR [95% CI]; p-value[d]
Side effects					
Specific AEs					
Immune-related AEs				No usable data	
Immune-related SAEs				No usable data	
Immune-related severe AEs (CTCAE grade ≥ 3)	609	38 (6.2)	578	6 (1.0)	6.01 [2.56; 14.11]; < 0.001
Pneumonia (SAE)	609	19 (3.1)	578	34 (5.9)	0.53 [0.31; 0.92]; 0.022
Respiratory, thoracic and mediastinal disorders (SAE)	609	64 (10.5)	578	31 (5.4)	1.96 [1.30; 2.96]; 0.001
Blood and lymphatic system disorders (CTCAE grade ≥ 3, SOC)	609	24 (3.9)	578	160 (27.7)	0.14 [0.09; 0.22]; < 0.001
- Including: febrile neutropenia (CTCAE grade ≥ 3, PT)	609	1 (0.2)	578	62 (10.7)	0.02 [0.00; 0.11]; < 0.001
Gastrointestinal disorders (CTCAE grade ≥ 3)	609	25 (4.1)	578	41 (7.1)	0.58 [0.36; 0.94]; 0.025
Musculoskeletal and connective tissue disorders (CTCAE grade ≥ 3)	609	29 (4.8)	578	12 (2.1)	2.29 [1.18; 4.45]; 0.012
	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[c]**
Alopecia	609	ND 3 (0.5)	578	ND 204 (35.3)	0.01 [0.00; 0.03]; < 0.001

(continued)

Table 14: Results – RCT, direct comparison: atezolizumab vs. docetaxel (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 the score by 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 [5]]).
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; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

From the available data, at most indications, e.g. of an added benefit, can be derived for overall survival based on the total population, and initially at most hints for all other outcomes due to the high risk of bias.

Mortality

Overall survival

The OAK study showed a statistically significant difference in favour of atezolizumab in comparison with docetaxel for the outcome "overall survival".

In addition, there was an effect modification by the characteristic "PD-L1 status" (TC3 or IC3 versus TC0/1/2 and IC0/1/2) for this outcome (see Section 2.3.2.4). This resulted in an indication of an added benefit of atezolizumab in comparison with docetaxel for patients with high PD-L1 expression (TC3 or IC3). For patients with low PD-L1 expression (TC0/1/2 and IC0/1/2), there was no hint of an added benefit of atezolizumab in comparison with docetaxel; an added benefit is not proven for these patients.

This deviates from the assessment of the company insofar as the company derived proof of added benefit for the outcome "all-cause mortality" based on the primary analysis population (N = 850) and the primary data cut-off (7 July 2016) for the total population irrespective of PD-L1 status.

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. Below, first the symptom outcomes with statistically significant group differences are described.

Haemoptysis, pain (chest), sore mouth, dysphagia, peripheral neuropathy, alopecia

A statistically significant difference in favour of atezolizumab in comparison with docetaxel was shown for each of the following outcomes: haemoptysis, pain (chest), sore mouth, dysphagia, peripheral neuropathy, and alopecia.

In addition, there was an effect modification by the characteristic "histology" for each of the outcomes "pain (chest)" and "peripheral neuropathy". Since the effect modification for this characteristic showed no consistent advantage or disadvantage of a treatment in a subgroup for different outcomes (including the quality of life functional scales), it is not considered further for the derivation of the added benefit (see Section 2.3.2.4).

The certainty of the result of the outcome "alopecia" was upgraded to an indication due to the size of the effect and the number of observed events for this outcome. This resulted in an indication of an added benefit of atezolizumab in comparison with docetaxel for this outcome and in a hint of an added benefit of atezolizumab for each of the remaining 5 outcomes.

Based on the primary analysis population and the primary data cut-off of the OAK study, the company derived proof of an added benefit for each of these outcomes.

Diarrhoea, appetite loss

A statistically significant difference in favour of atezolizumab in comparison with docetaxel was shown for each of the outcomes "diarrhoea" and "appetite loss".

There was an effect modification by the characteristic "PD-L1 status" for both outcomes.

For the outcome "diarrhoea", a statistically significant difference in favour of atezolizumab was shown both for patients with high PD-L1 expression (TC3 or IC3) and for patients with lower PD-L1 expression (TC0/1/2 and IC0/1/2). This resulted in a hint of an added benefit of atezolizumab in comparison with docetaxel for these patients. The effect modification is reflected in different extents of the added benefit for this outcome, however (see Section 2.3.4.1).

For the outcome "appetite loss", a statistically significant difference in favour of atezolizumab was shown for patients with high PD-L1 expression (TC3 or IC3). This resulted in a hint of an added benefit of atezolizumab in comparison with docetaxel for these patients. In contrast, there was no statistically significant difference between the treatment groups for patients with lower PD-L1 expression (TC0/1/2 and IC0/1/2). For patients with lower PD-L1 expression (TC0/1/2 and IC0/1/2), this resulted in no hint of an added benefit of atezolizumab in comparison with docetaxel; hence an added benefit is not proven.

This deviates from the assessment of the company, which derived proof of an added benefit of atezolizumab for the outcome "diarrhoea" for the total population based on the primary analysis population and the primary data cut-off of the OAK study, and no added benefit for the outcome "appetite loss".

Nausea and vomiting

A statistically significant difference in favour of atezolizumab in comparison with docetaxel was shown for the outcome "nausea and vomiting". The extent of the added benefit for this outcome from the category "non-serious/non-severe symptoms/late complications" was no more than marginal. Hence there was no hint of an added benefit of atezolizumab in comparison with docetaxel; an added benefit is therefore not proven.

This does not concur with the assessment of the company, which derived proof of an added benefit of atezolizumab in comparison with docetaxel for this outcome based on the primary analysis population and the primary data cut-off of the OAK study.

Further symptom outcomes

No statistically significant differences between the treatment groups were shown for any further symptom outcomes. Hence there was no hint of an added benefit of atezolizumab in comparison with docetaxel for any further symptom outcomes; an added benefit is therefore not proven.

This concurs with the company's assessment based on the primary analysis population and the primary data cut-off of the OAK study.

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. There was an effect modification by the characteristic "histology" for each of the outcomes "physical functioning" and "global health status". Since the effect modification for this characteristic showed no consistent advantage or disadvantage of a treatment in a subgroup for different outcomes (including the quality of life functional scales), it is not considered further for the derivation of the added benefit (see Section 2.3.2.4). Hence there was no hint of an added benefit for the outcomes of health-related quality of life; an added benefit is not proven for these outcomes.

This concurs with the company's assessment based on the primary analysis population and the primary data cut-off of the OAK study.

Side effects

Serious adverse events

A statistically significant difference in favour of atezolizumab between the treatment groups was shown for the outcome "SAEs".

In addition, there was an effect modification by the characteristics "PD-L1 status" and "age" for the outcome "SAEs". As described in Section 2.3.2.4, the characteristic "age" was not

considered further in this situation. A statistically significant difference in favour of atezolizumab was shown for patients with high PD-L1 expression (TC3 or IC3). This resulted in a hint of lesser harm of atezolizumab in comparison with docetaxel for these patients. There was no statistically significant difference between the treatment groups for patients with lower PD-L1 expression (TC0/1/2 and IC0/1/2). This resulted in no hint of lesser harm of atezolizumab in comparison with docetaxel for these patients; lesser harm is therefore not proven for patients with lower PD-L1 expression (TC0/1/2 and IC0/1/2).

This deviates from the assessment of the company, which did not consider the effect modification and derived proof of an added benefit of atezolizumab for this outcome for the total population.

Severe adverse events (CTCAE grade ≥ 3), discontinuation due to adverse events

A statistically significant difference in favour of atezolizumab between the treatment groups was shown for each of the outcomes "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". This resulted in a hint of lesser harm of atezolizumab in comparison with docetaxel for each of these outcomes.

The company derived proof of an added benefit for both outcomes.

Specific adverse events

Immune-related severe adverse events (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of atezolizumab in comparison with docetaxel was shown for the outcome "immune-related severe AEs (CTCAE grade ≥ 3)". The certainty of the result of this outcome was upgraded to an indication due to the size of the effect and the number of observed events. This resulted in an indication of greater harm of atezolizumab in comparison with docetaxel.

The company did not use this outcome for the derivation of the added benefit in its assessment.

Further specific adverse events

A statistically significant difference in favour of atezolizumab in comparison with docetaxel was shown for each of the following further specific AE outcomes chosen: alopecia, pneumonia, blood and lymphatic system disorders, febrile neutropenia, and gastrointestinal disorders. The certainty of the results of the AE outcomes "alopecia" and "blood and lymphatic system disorders" (including the Preferred Term [PT] "febrile neutropenia") was upgraded to an indication due to the size of the effects and the number of observed events for these outcomes. This resulted in an indication of lesser harm of atezolizumab in comparison with docetaxel for each of these outcomes. There was a hint of lesser harm of atezolizumab for each of the remaining 2 outcomes.

The company did not use these outcomes in its assessment.

There was statistically significant difference to the disadvantage of atezolizumab in comparison with docetaxel for each of the specific AE outcomes “respiratory, thoracic and mediastinal disorders” and “musculoskeletal and connective tissue disorders”. This resulted in a hint of greater harm of atezolizumab in comparison with docetaxel for each of these outcomes.

The company also did not use these outcomes in its assessment.

2.3.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present assessment:

- age (< 65 years, ≥ 65 years)
- sex (men, women)
- ethnicity (white, Asian, other)
- smoking status (never-smoker, current/former)
- histology (squamous, non-squamous)
- brain metastases (yes/no)
- PD-L1 status (TC3 or IC3, TC0/1/2 and IC0/1/2)

In its dossier, the company presented subgroup analyses on most outcomes and for the different data cut-offs and populations; subgroup analyses for the secondary analysis population and the secondary data cut-off of the OAK study, which were relevant for the assessment, can be found in additional analyses in Module 5 of the dossier.

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

Handling of subgroup analyses in the present assessment situation

Hereinafter, interactions within the outcome categories of symptoms and health-related quality of life are only presented if an effect modification is shown for at least 2 outcomes for a subgroup characteristic within an outcome category.

PD-L1 status as relevant effect modifier

With its dossier, the company presented a total of 8 different operationalizations of the PD-L1 status as subgroup characteristic, which considered both the TC level and the IC level individually and combinations of TC and IC level (see Section 2.6.2.4.3 of the full dossier assessment). Since it became apparent in the course of the study that not only the PD-L1 expression on the immune cells (IC), but also PD-L1 expression on the tumour cells (TC) plays a role, it is meaningful with regard to content to use a combination of both

characteristics as subgroup characteristic. Furthermore, the statistical analysis plan mandated combined subgroup analyses for the subgroups TC3 or IC3 (PD-L1 expression ≥ 50% of the tumour cells or ≥ 10% of the immune cells), TC2/3 or IC2/3 (PD-L1 expression ≥ 5% of the tumour cells or ≥ 5% of the immune cells) and TC1/2/3 or IC1/2/3 (PD-L1 expression ≥ 1% of the tumour cells or ≥ 1% of the immune cells). Consideration of the results on the outcome "overall survival" showed that the PD-L1 status was relevant for this outcome (see Table 15).

Table 15: PD-L1 status subgroup (mortality, time to event) – RCT, direct comparison: atezolizumab vs. docetaxel

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
OAK						
Mortality						
PD-L1 status[a]						
TC3 or IC3	88	20.5 [16.3; 30.2] 51 (58.0)	85	9.7 [7.9; 11.6] 65 (76.5)	0.48 [0.33; 0.69]	< 0.001
TC0/1/2 and IC0/1/2	517	12.3 [10.2; 14.0] 368 (71.2)	523	9.8 [8.7; 11.5] 374 (71.5)	0.87 [0.76; 1.01]	0.064
Unknown	8	14.3 [8.5; NC] 5 (62.5)	4	9.7 [8.4; 10.9] 2 (50.0)	0.33 [0.05; 2.05]	0.214
					Interaction:	0.004[b]
TC2/3 or IC2/3	167	16.3 [13.5; 19.9] 107 (64.1)	182	11.4 [9.3; 12.9] 128 (70.3)	0.68 [0.52; 0.88]	
TC0/1 and IC0/1	437	11.8 [10.1; 14.0] 312 (71.4)	425	9.3 [8.2; 11.0] 310 (72.9)	0.86 [0.73; 1.00]	
Unknown	9	15.7 [11.3; NC] 5 (55.6)	5	8.4 [6.9; 10.9] 3 (60.0)	0.15 [0.02; 0.91]	
					Interaction:	0.154[b]
TC1/2/3 or IC1/2/3	346	14.3 [12.4; 16.6] 231 (66.8)	337	10.8 [9.3; 12.0] 234 (69.4)	0.77 [0.64; 0.92]	
TC0 and IC0	260	11.8 [9.9; 14.1] 188 (72.3)	271	8.9 [7.9; 11.3] 204 (75.3)	0.84 [0.69; 1.03]	
Unknown	7	11.3 [8.5; NC] 5 (71.4)	4	8.4 [6.9; 10.9] 3 (75.0)	0.29 [0.06; 1.48]	
					Interaction:	0.498[b]

a: The different operationalizations concur with the analyses prespecified by the company.
b: p-value: likelihood ratio test in an unstratified analysis using the Cox proportional hazards model.
CI: confidence interval; HR: hazard ratio; IC: immune cells; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; TC: tumour cells; vs.: versus

A large effect of atezolizumab in overall survival was shown in the subgroup with high PD-L1 status (TC3 or IC3) as well as an effect modification of this subgroup with the subgroup with lower status (TC0/1/2 and IC0/1/2). The results presented in the table show that the observed effect becomes smaller if patients in the group with the highest PD-L1 status (TC3 or IC3) are pooled with those with medium PD-L1 status (TC1/2 and IC1/2). The most notable change was already shown on inclusion of the patients with TC2 or IC2 (Figure 1). Conversely, the observed effect remained practically unchanged if the patient group with the lowest PD-L1 status (TC0 and IC0) was pooled with the patient group with a medium expression status (TC1/2 and IC1/2).

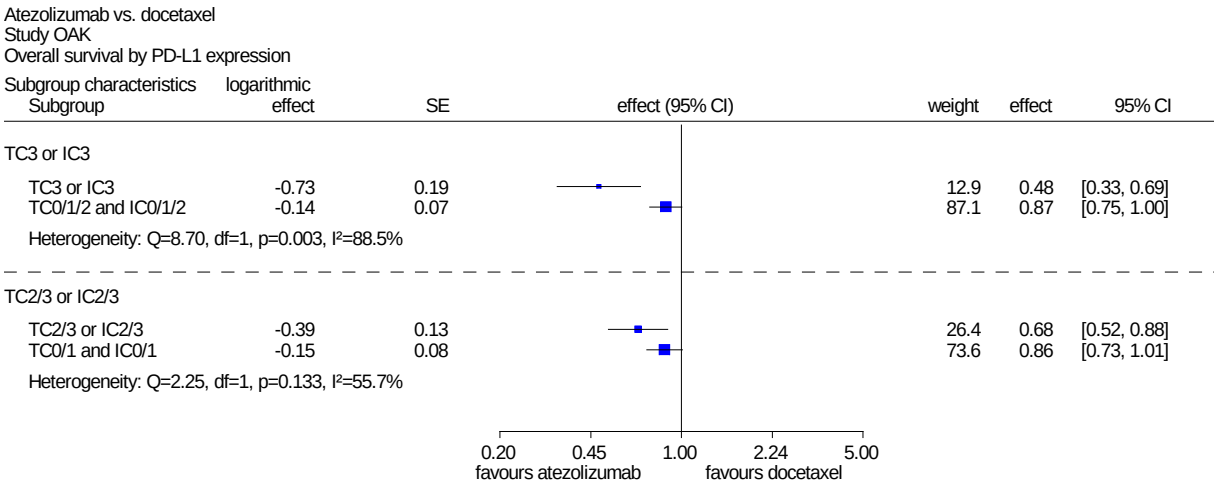

Figure 1: Subgroup analysis by PD-L1 status for overall survival – RCT, direct comparison: atezolizumab vs. docetaxel

Overall, a suitable threshold for this subgroup characteristic between TC3 or IC3 on the one hand, and TC0/1/2 and IC0/1/2 on the other, can be derived from the available analyses.

In addition, there were 4 relevant interactions for the operationalization TC3 or IC3 versus TC0/1/2 and IC0/1/2. Hence the present assessment used the characteristic “PD-L1 status” for the derivation of the added benefit in the presence of an effect modification.

Table 16, Table 17 and Table 18 summarize the subgroup results on the comparison of atezolizumab with docetaxel in the OAK study.

Table 16: Subgroups (mortality, side effects, time to event) – RCT, direct comparison: atezolizumab vs. docetaxel

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
OAK						
Mortality						
PD-L1 status						
TC3 or IC3	88	20.5 [16.3; 30.2] 51 (58.0)	85	9.7 [7.9; 11.6] 65 (76.5)	0.48 [0.33; 0.69]	< 0.001
TC0/1/2 and IC0/1/2	517	12.3 [10.2; 14.0] 368 (71.2)	523	9.8 [8.7; 11.5] 374 (71.5)	0.87 [0.76; 1.01]	0.064
Unknown	8	14.3 [8.5; NA] 5 (62.5)	4	9.7 [8.4; 10.9] 2 (50.0)	0.33 [0.05; 2.05]	0.214
					Interaction:	0.004[b]
Side effects						
SAEs						
Age						
< 65	334	ND 108 (32.3)	312	ND 78 (25.0)	1.00 [0.74; 1.35]	0.990
≥ 65	275	ND 87 (31.6)	266	ND 102 (38.3)	0.55 [0.41; 0.75]	< 0.001
					Interaction:	0.007[b]
PD-L1 status						
TC3 or IC3	88	ND 22 (25.0)	81	ND 34 (42.0)	0.29 [0.16; 0.53]	< 0.001
TC0/1/2 and IC0/1/2	513	ND 170 (33.1)	494	ND 146 (29.6)	0.86 [0.69; 1.09]	0.207
Unknown	8	ND 3 (37.5)	3	ND ND	–[a]	0.540
					Interaction:	0.002[b]

a: Effect estimation not meaningfully interpretable.
b: p-value: likelihood ratio test in an unstratified analysis using the Cox proportional hazards model.
CI: confidence interval; HR: hazard ratio; IC: immune cells; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; TC: tumour cells; vs.: versus

Table 17: Subgroups (morbidity, time to event) – RCT, direct comparison: atezolizumab vs. docetaxel

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
OAK						
Morbidity						
Symptoms (EORTC QLQ-C30 symptom scales) – time to deterioration						
Diarrhoea						
PD-L1 status						
TC3 or IC3	89	17.0 [9.8; NC] 28 (31.5)	80	2.2 [1.5; 4.2] 39 (48.8)	0.29 [0.16; 0.54]	< 0.001
TC0/1/2 and IC0/1/2	513	10.9 [8.3; 16.6] 164 (32.0)	491	4.4 [4.0; 6.7] 180 (36.7)	0.65 [0.52; 0.81]	< 0.001
Unknown	7	3.6 [2.4; NC] 3 (42.9)	3	0.8 [0.8; 0.9] 2 (66.7)	–[a]	0.225
					Interaction:	0.017[b]
Appetite loss						
PD-L1 status						
TC3 or IC3	89	7.9 [6.2; 14.3] 38 (42.7)	80	2.8 [1.5; 4.0] 46 (57.5)	0.36 [0.22; 0.61]	< 0.001
TC0/1/2 and IC0/1/2	513	3.6 [2.8; 5.0] 259 (50.5)	493	3.5 [2.8; 4.3] 223 (45.2)	0.92 [0.76; 1.11]	0.367
Unknown	7	1.5 [0.9; NC] 5 (71.4)	3	0.8 [0.8; 0.9] 2 (66.7)	–[a]	0.225
					Interaction:	0.005[b]
Symptoms (EORTC QLQ-LC13 symptom scales) – time to deterioration						
Pain (chest)						
Histology						
Non-squamous	448	15.2 [7.2; 21.9] 154 (34.4)	422	8.6 [5.8; NC] 134 (31.8)	0.85 [0.67; 1.09]	0.199
Squamous	160	14.5 [11.9; NC] 44 (27.5)	153	3.5 [2.8; 4.7] 57 (37.3)	0.42 [0.27; 0.65]	< 0.001
					Interaction:	0.004[b]
Neuropathy peripheral						
Histology						
Non-squamous	448	8.6 [6.4; 13.9] 162 (36.2)	422	3.0 [2.8; 3.5] 209 (49.5)	0.50 [0.41; 0.62]	< 0.001
Squamous	160	4.9 [3.6; 7.2] 70 (43.8)	154	3.3 [2.8; 4.4] 60 (39.0)	0.82 [0.57; 1.18]	0.286
					Interaction:	0.025[b]

(continued)

Table 17: Subgroups (morbidity, time to event) – RCT, direct comparison: atezolizumab vs. docetaxel (continued)

a: Effect estimation not meaningfully interpretable.
b: 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).

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; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; TC: tumour cells; vs.: versus

Table 18: Subgroups (health-related quality of life, time to event) – RCT, direct comparison: atezolizumab vs. docetaxel

Study	**Atezolizumab**		**Docetaxel**		**Atezolizumab vs. docetaxel**	
Outcome **Characteristic** **Subgroup**	**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**
Study OAK						
Health-related quality of life (EORTC QLQ-C30 functional scales) – time to deterioration						
Physical functioning						
Histology						
Non-squamous	449	2.8 [2.2; 4.1] 236 (52.6)	422	3.1 [2.8; 3.7] 204 (48.3)	0.99 [0.81; 1.20]	0.882
Squamous	160	3.4 [2.3; 4.9] 85 (53.1)	155	1.9 [1.5; 2.8] 93 (60.0)	0.60 [0.44; 0.83]	0.002
					Interaction:	0.009[a]
Global health status						
Histology						
Non-squamous	449	2.4 [2.1; 2.9] 262 (58.4)	422	2.5 [2.1; 3.0] 221 (52.4)	1.01 [0.84; 1.22]	0.875
Squamous	160	3.5 [2.8; 5.0] 83 (51.9)	153	2.3 [2.0; 3.1] 75 (49.0)	0.65 [0.46; 0.91]	0.013
					Interaction:	0.024[a]

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).

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

Mortality

Overall survival

As shown above, there was an effect modification by the characteristic “PD-L1 status” for the outcome “mortality”.

A statistically significant difference in favour of atezolizumab was shown for patients with high PD-L1 expression (TC3 or IC3). This resulted in an indication of an added benefit in comparison with docetaxel for patients with high PD-L1 expression (TC3 or IC3). There was no statistically significant difference between the treatment groups for patients with low PD-L1 expression (TC0/1/2 and IC0/1/2). For patients with low PD-L1 expression (TC0/1/2 and IC0/1/2), this resulted in no hint of an added benefit of atezolizumab in comparison with docetaxel; hence an added benefit is not proven for these patients.

This deviates from the assessment of the company, which derived proof of an added benefit in overall survival for the total population based on the primary analysis population and the primary data cut-off. The company identified no relevant effect modification in this data situation.

Side effects

Serious adverse events

In addition, there was an effect modification by the characteristics “age” and “PD-L1 status” for the outcome “SAEs”. There were no data on the investigation of possible dependencies between the subgroup characteristics. Since consistent effect modification for the characteristic “PD-L1 status” was shown for 4 outcomes, this characteristic was used for the assessment, whereas the characteristic “age” was not considered further.

For the characteristic “PD-L1 status”, a statistically significant difference in favour of atezolizumab versus docetaxel was shown for patients with high PD-L1 expression (TC3 or IC3). This resulted in a hint of lesser harm of atezolizumab in comparison with docetaxel for patients with high PD-L1 expression (TC3 or IC3). In contrast, there was no statistically significant difference between the treatment groups for patients with low PD-L1 expression (TC0/1/2 and IC0/1/2). This resulted in no hint of greater or lesser harm of atezolizumab in comparison with docetaxel for patients with low PD-L1 expression (TC0/1/2 and IC0/1/2); greater or lesser harm is therefore not proven for patients with low PD-L1 expression (TC0/1/2 and IC0/1/2).

This resulted in a hint of lesser harm of atezolizumab in comparison with docetaxel for patients with high PD-L1 expression (TC3 or IC3) for the outcome “SAEs”: This deviates from the assessment of the company, which identified no relevant interactions for AE outcomes.

Morbidity

Symptoms (EORTC QLQ-C30)

There was an effect modification by the characteristic "PD-L1 status" for the outcome "diarrhoea" (time to deterioration). A statistically significant difference in favour of atezolizumab was shown both for patients with high PD-L1 expression (TC3 or IC3) and for patients with low PD-L1 expression (TC0/1/2 and IC0/1/2). This resulted in a hint of an added benefit of atezolizumab in comparison with docetaxel for both subgroups. The effect modification is reflected in different extents of the added benefit for this outcome, however (see Section 2.3.4.1).

There was an effect modification by the characteristic "PD-L1 status" also for the outcome "appetite loss" (time to deterioration). A statistically significant difference in favour of atezolizumab was shown for patients with high PD-L1 expression (TC3 or IC3). This resulted in a hint of an added benefit of atezolizumab in comparison with docetaxel for these patients. There was no statistically significant difference between the treatment groups for patients with low PD-L1 expression (TC0/1/2 and IC0/1/2). For patients with unknown or low PD-L1 expression (TC0/1/2 and IC0/1/2), this resulted in no hint of an added benefit of atezolizumab in comparison with docetaxel; hence an added benefit is not proven for these patients.

This deviates from the approach of the company, which identified no relevant effect modification for morbidity outcomes based on the primary analysis population and the primary data cut-off.

Symptoms (EORTC QLQ-LC13)

There was an effect modification by the characteristic "histology" for each of the outcomes "pain (chest)" (time to deterioration) and "peripheral neuropathy" (time to deterioration). These were inconsistent. A statistically significant difference in favour of atezolizumab was shown for the outcome "pain (chest)" for patients with squamous histology of the tumour, which was not shown for patients with non-squamous histology. For the outcome "peripheral neuropathy", in contrast, a statistically significant difference in favour of atezolizumab was shown for patients with non-squamous histology of the tumour, which was not shown for patients with squamous histology. Due to the missing consistency of the results, they were not considered further for the derivation of the added benefit.

This concurs with the assessment of the company, which also derived no subgroup-specific conclusions for these 2 outcomes based on the primary analysis population and the primary data cut-off.

Health-related quality of life

There was an effect modification by the characteristic "histology" for each of the outcomes "physical functioning" (time to deterioration) and "global health status" (time to deterioration). A statistically significant difference in favour of atezolizumab was shown for

patients with squamous histology of the tumour. Since the direction of the effect modification in the symptom outcomes was not consistent, the observed effect modifications on health-related quality of life for the characteristic "histology" were also not considered further.

This concurs with the assessment of the company, which derived no subgroup-specific conclusions on health-related quality of life based on the primary analysis population and the primary data cut-off.

2.3.3 Estimation of the influence of the POPLAR study on the result of the benefit assessment

As shown in Section 2.3.1, the company neither included the POPLAR study, which was relevant for the present research question, in the study pool, nor did it present all data on this study relevant for the benefit assessment in the dossier. The company drew its conclusions on the added benefit exclusively on the basis of the data of the OAK study. With 81%, this study comprised the notably larger proportion of the patients relevant for the research question. Hereinafter, the influence of the results of the POPLAR study on the result of the benefit assessment is estimated in qualitative terms on the basis of the available data.

Mortality – overall survival

A statistically significant advantage in favour of atezolizumab in comparison with treatment with docetaxel for the outcome "overall survival" was also shown for the total population of the POPLAR study (data cut-off 8 May 2015, HR: 0.73; 95% confidence interval (CI): [0.53; 0.99]; p = 0.040). As in the OAK study, a notably larger effect was shown in the subgroup of patients with high PD-L1 status (TC3 or IC3); HR: 0.49; 95% CI: [0.22; 1.07]; p: 0.068). With a notably smaller number of patients than in the OAK study, the effect estimates of both studies were consistent. Against this background, it can be excluded that the advantage of atezolizumab in patients with high PD-L1 status found in the OAK study is challenged by the data from the POPLAR study. Instead, the data confirmed the effects and their extent observed in the OAK study.

Side effects – serious adverse events, severe adverse events (CTCAE grade ≥ 3) and discontinuation due to adverse events

No event time analyses for the AE outcomes were available for the POPLAR study. The available naive frequencies on SAEs, severe AEs, and discontinuations due to AEs showed no signs that would raise general doubts about the effects found. The size of the effects was unclear due to a lack of time-adjusted analyses, however.

Certainty of results

The qualitative consideration of individual outcomes of the POPLAR study showed that the results of the OAK study are not principally questioned. Due to the incompleteness of the data of the POPLAR study, this did not change the assessment of the certainty of results, however.

It remains open whether presence of complete data including a meta-analysis of the 2 studies OAK and POPLAR would result in a higher certainty of results.

2.3.4 Probability and extent of added benefit

The derivation of probability and extent of added benefit for research question 1 (patients for whom treatment with docetaxel, pemetrexed or nivolumab is indicated) at outcome level is shown below, taking into account the various outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on 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.

2.3.4.1 Assessment of added benefit at outcome level

The severity grade has to be assessed for the outcomes of the categories “morbidity” (symptoms) and “side effects” to determine the extent of the added benefit at outcome level. For individual outcomes, the severity grade resulted directly from their respective operationalization (severe AEs and SAEs). For individual outcomes of the category of side effects and the morbidity outcomes (symptoms), the severity grade did not result directly from the operationalization and had to be determined in the present study situation.

The severity grade of the following symptoms of the EORTC QLQ-C30 or the EORTC QLQ-LC13 was assessed using the results by CTCAE severity grade on AEs observed in the OAK study: diarrhoea, appetite loss, haemoptysis, pain (chest), sore mouth, dysphagia, peripheral neuropathy, and alopecia. The AEs were mostly non-severe (CTCAE grade 1 and 2). The symptoms were therefore classified as “non-serious”.

For the outcome “discontinuation due to AEs”, the proportion of discontinuations due to SAEs was 47%, constituting less than half of the discontinuations. The outcome was therefore also allocated to the category “non-serious”.

The following Table 19 describes the extent of added benefit at outcome level for research question 1, based on the data availability of the OAK study presented in Section 2.3.2.

Table 19: Extent of added benefit at outcome level: atezolizumab vs. docetaxel

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Atezolizumab vs. docetaxel** **Median time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival PD-L1 status TC3 or IC3	Median: 20.5 vs. 9.7 months HR: 0.48 [0.33; 0.69]; p < 0.001 probability: "indication"	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: "major"
TC0/1/2 and IC0/1/2	Median: 12.3 vs. 9.8 months HR: 0.87 [0.76; 1.01]; p = 0.064	Lesser benefit/added benefit not proven
Morbidity		
Symptoms (EORTC QLQ-C30 symptom scales) – time to deterioration[c]		
Nausea and vomiting	Median: 6.9 vs. 4.4 months HR: 0.83 [0.69; 0.999]; p = 0.049	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[d]
Diarrhoea PD-L1 status TC3 or IC3	Median: 17.0 vs. 2.2 months HR: 0.29 [0.16; 0.54]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
TC0/1/2 and IC0/1/2	Median: 10.9 vs. 4.4 months HR: 0.65 [0.52; 0.81]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"

(continued)

Table 19: Extent of added benefit at outcome level: atezolizumab vs. docetaxel (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Atezolizumab vs. docetaxel** **Median time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Morbidity		
Symptoms (EORTC QLQ-C30 symptom scales) – time to deterioration[c]		
Appetite loss PD-L1 status TC3 or IC3	Median: 7.9 vs. 2.8 months HR: 0.36 [0.22; 0.61]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
TC0/1/2 and IC0/1/2	Median: 3.6 vs. 3.5 months HR: 0.92 [0.76; 1.11]; p = 0.367	Lesser benefit/added benefit not proven
Dyspnoea	Median: 4.6 vs. 3.8 months HR: 0.93 [0.77; 1.11]; p = 0.407	Lesser benefit/added benefit not proven
Fatigue	Median: 1.4 vs. 1.4 months HR: 0.92 [0.80; 1.07]; p = 0.272	Lesser benefit/added benefit not proven
Insomnia	Median: 4.9 vs. 4.7 months HR: 1.00 [0.84; 1.21]; p = 0.959	Lesser benefit/added benefit not proven
Pain	Median: 2.8 vs. 2.8 months HR: 0.88 [0.75; 1.03]; p = 0.130	Lesser benefit/added benefit not proven
Constipation	Median: 5.0 vs. 4.9 months HR: 1.03 [0.86; 1.24]; p = 0.740	Lesser benefit/added benefit not proven
Symptoms (EORTC QLQ-LC13 symptom scales) – time to deterioration[c]		
Haemoptysis	Median: NA vs. 25.1 months HR: 0.64 [0.48; 0.87]; p = 0.004 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Pain (chest)	Median: 15.2 vs. 6.4 months HR: 0.72 [0.59; 0.89]; p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"

(continued)

Table 19: Extent of added benefit at outcome level: atezolizumab vs. docetaxel (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Atezolizumab vs. docetaxel** **Median time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Morbidity		
Symptoms (EORTC QLQ-LC13 symptom scales) – time to deterioration[c]		
Sore mouth	Median: 16.6 vs. 4.2 months HR: 0.45 [0.37; 0.56]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Dysphagia	Median: 15.7 vs. 8.6 months HR: 0.69 [0.56; 0.86]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Neuropathy peripheral	Median: 7.0 vs. 3.0 months HR: 0.57 [0.47; 0.68]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Alopecia	Median: NA vs. 0.8 months HR: 0.06 [0.05; 0.08]; p < 0.001 probability: "indication"[e]	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Dyspnoea	Median: 1.7 vs. 1.9 months HR: 0.96 [0.82; 1.11]; p = 0.570	Lesser benefit/added benefit not proven
Cough	Median: 5.5 vs. 6.0 months HR: 1.10 [0.90; 1.33]; p = 0.350	Lesser benefit/added benefit not proven
Pain (arm/shoulder)	Median: 7.2 vs. 7.7 months HR: 1.01 [0.83; 1.24]; p = 0.901	Lesser benefit/added benefit not proven
Pain (other)	Median: 3.8 vs. 4.1 months HR: 0.91 [0.76; 1.09]; p = 0.313	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 functional scales – time to deterioration[c]		
Physical functioning	Median: 2.9 vs. 2.9 months HR: 0.86 [0.73; 1.02]; p = 0.080	Lesser benefit/added benefit not proven
Emotional functioning	Median: 6.9 vs. 5.1 months HR: 0.90 [0.74; 1.09]; p = 0.267	Lesser benefit/added benefit not proven
Cognitive functioning	Median: 3.5 vs. 3.6 months HR: 1.01 [0.85; 1.20]; p = 0.925	Lesser benefit/added benefit not proven

(continued)

Table 19: Extent of added benefit at outcome level: atezolizumab vs. docetaxel (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Atezolizumab vs. docetaxel** **Median time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
EORTC QLQ-C30 functional scales – time to deterioration[c]		
Social functioning	Median: 3.5 vs. 2.6 months HR: 0.86 [0.73; 1.02]; p = 0.075	Lesser benefit/added benefit not proven
Global health status	Median: 2.8 vs. 2.4 months HR: 0.92 [0.78; 1.08]; p = 0.295	Lesser benefit/added benefit not proven
Role functioning	Median: 2.1 vs. 2.1 months HR: 0.87 [0.74; 1.01]; p = 0.068	Lesser benefit/added benefit not proven
Side effects		
SAEs PD-L1 status TC3 or IC3	Median: ND vs. ND HR: 0.29 [0.16; 0.53]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% lesser harm, extent: "major"
TC0/1/2 and IC0/1/2	Median: ND vs. ND HR: 0.86 [0.69; 1.09]; p = 0.207	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	Median: ND vs. ND HR: 0.41 [0.34; 0.49]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% lesser harm, extent: "major"
Discontinuation due to AEs	Proportion of events: 7.9% vs. 18.3% RR: 0.43 [0.31; 0.59]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
Specific AEs		
Immune-related AEs	No usable data	
Immune-related SAEs	No usable data	

(continued)

Table 19: Extent of added benefit at outcome level: atezolizumab vs. docetaxel (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Atezolizumab vs. docetaxel** **Median time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
Immune-related severe AEs (CTCAE grade ≥ 3)	Proportion of events: 6.2% vs. 1.0% RR: 6.01 [2.56; 14.11]; p < 0.001 RR: 0.17 [0.07; 0.39][f] probability: "indication"[e]	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: "major"
Alopecia	Median: ND vs. ND HR: 0.01 [0.00; 0.03]; p < 0.001 probability: "indication"[e]	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
Pneumonia	Proportion of events: 3.1% vs. 5.9% RR: 0.53 [0.31; 0.92]; p = 0.022 probability: "hint"	Outcome category: serious/severe side effects 0.90 ≤ CI_u < 1.00 lesser harm, extent: "minor"
Respiratory, thoracic and mediastinal disorders	Proportion of events: 10.5% vs. 5.4% RR: 1.96 [1.30; 2.96]; p = 0.001 RR: 0.51 [0.34; 0.77][f] probability: "hint"	Outcome category: serious/severe side effects 0.75 ≤ CI_u < 0.90 greater harm, extent: "considerable"
Blood and lymphatic system disorders (SOC)	Proportion of events: 3.9% vs. 27.7% RR: 0.14 [0.09; 0.22]; p < 0.001 probability: "indication"[e]	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% lesser harm, extent: "major"
Including: febrile neutropenia (PT)	Proportion of events: 0.2% vs. 10.7% RR: 0.02 [0.00; 0.11]; p < 0.001 probability: "indication"[e]	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% lesser harm, extent: "major"
Gastrointestinal disorders	Proportion of events: 4.1% vs. 7.1% RR: 0.58 [0.36; 0.94]; p = 0.025 probability: "hint"	Outcome category: serious/severe side effects 0.90 ≤ CI_u < 1.00 lesser harm, extent: "minor"
Musculoskeletal and connective tissue disorders	Proportion of events: 4.8% vs. 2.1% RR: 2.29 [1.18; 4.45]; p = 0.012 RR: 0.44 [0.22; 0.85][f] probability: "hint"	Outcome category: serious/severe side effects 0.75 ≤ CI_u < 0.90 greater harm, extent: "considerable"
The results are from the OAK study; the company did not consider the POPLAR study, which is also relevant, in its study pool.		

(continued)

Table 19: Extent of added benefit at outcome level: atezolizumab vs. docetaxel (continued)

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: 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 the score by at least 2 consecutive cycles, or an initial increase was followed by the patient's death within 3 weeks.
d: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
e: The certainty of the result of this outcome was rated as high due to the size of the effect and the number of observed events.
f: Institute's calculation: reversed direction of effect to enable use of limits to derive the extent of the added benefit.

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; HR: hazard ratio; IC: immune cells; NA: not achieved; ND: no data; PD-L1: programmed cell death ligand 1; 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; TC: tumour cells; vs.: versus

2.3.4.2 Overall conclusion on added benefit

Since PD-L1 status was a relevant effect modifier consistent across several outcomes, the overall conclusion on the added benefit is derived separately for patients with high and for patients with low PD-L1 status.

Patients with high PD-L1 status (TC3 or IC3)

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 in comparison with docetaxel – subgroup of patients with high PD-L1 status (TC3 or IC3)

Positive effects	**Negative effects**
Mortality ▪ overall survival: indication of an added benefit – extent: "major"	–
Non-serious/non-severe symptoms/late complications ▪ symptoms: hint of an added benefit – extent: "considerable" (including diarrhoea, appetite loss, sore mouth, peripheral neuropathy) ▪ symptoms: indication of an added benefit – extent: "considerable" (including alopecia) ▪ symptoms: hint of an added benefit – extent: "minor" (including haemoptysis, pain [chest], dysphagia)	–
Serious/severe side effects ▪ SAEs: hint of lesser harm – extent: "major" ▪ severe AEs (CTCAE grade ≥ 3): hint of lesser harm – extent: "major" ▪ specific AEs: indication of lesser harm – extent: "major" (including blood and lymphatic system disorders [SOC] with febrile neutropenia [PT]) ▪ specific AEs: hint of lesser harm – extent: "minor" (including pneumonia, gastrointestinal disorders)	Serious/severe side effects ▪ immune-related severe AEs (CTCAE grade ≥ 3): indication of greater harm – extent: "major" ▪ specific AEs: hint of greater harm – extent: "considerable" (including respiratory, thoracic and mediastinal disorders, musculoskeletal and connective tissue disorders)
Non-serious/non-severe side effects ▪ discontinuation due to AEs: hint of lesser harm – extent: "considerable" ▪ specific AEs: indication of lesser harm – extent: "considerable" (including alopecia)	–
The underlying results are from the OAK study; the company did not consider the POPLAR study, which is also relevant, in its study pool.	
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; IC: immune cells; PD-L1: programmed cell death ligand 1; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class; TC: tumour cells	

In the overall consideration, there were mostly positive effects of atezolizumab in comparison with docetaxel for patients with high PD-L1 status (TC3 or IC3).

On the positive side, there was an indication of major added benefit for the outcome "overall survival". In addition, there were hints or an indication of a minor or considerable added benefit for several symptom outcomes.

Positive effects outweighed negative effects also regarding side effects. Among other things, there was overall a hint of lesser harm of major extent for the outcomes "SAEs" and "severe AEs (CTCAE grade ≥ 3)". Regarding specific AEs, there were both positive effects (including febrile neutropenia) and negative effects (including immune-related severe AEs) of partly major extent. In the overall consideration, the negative effects outweighed neither the added benefit in general nor the extent of the added benefit because of the high number and the size

of the positive effects. Hence an indication of a major added benefit of atezolizumab can be derived from the results of the OAK study.

In the derivation of the overall conclusion on the added benefit, it has additionally to be taken into account in the present situation whether the results of the POPLAR study could have a relevant influence on the extent of the added benefit. As shown in Section 2.3.3, the results of the POPLAR study on overall survival support the effect of the OAK study. Even though the AE data were incomplete, the qualitative consideration did not raise general doubts about the results of the OAK study. Hence overall, an indication of major added benefit of atezolizumab in comparison with the ACT docetaxel was derived for patients with high PD-L1 status (TC3 or IC3).

Patients with low PD-L1 status (TC0/1/2 and IC0/1/2)

Table 21 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 21: Positive and negative effects from the assessment of atezolizumab in comparison with docetaxel – subgroup of patients with low PD-L1 status (TC0/1/2 and IC0/1/2)

Positive effects	**Negative effects**
Non-serious/non-severe symptoms/late complications ▪ symptoms: hint of an added benefit – extent: “considerable” (including sore mouth, peripheral neuropathy) ▪ symptoms: indication of an added benefit – extent: “considerable” (including alopecia) ▪ symptoms: hint of an added benefit – extent: “minor” (including diarrhoea, haemoptysis, pain [chest], dysphagia)	–
Serious/severe side effects ▪ severe AEs (CTCAE grade ≥ 3): hint of lesser harm – extent: “major” ▪ specific AEs: indication of lesser harm – extent: “major” (including blood and lymphatic system disorders [SOC] with febrile neutropenia [PT]) ▪ specific AEs: hint of lesser harm – extent: “minor” (including pneumonia, gastrointestinal disorders)	Serious/severe side effects ▪ immune-related severe AEs (CTCAE grade ≥ 3): indication of greater harm – extent: “major” ▪ specific AEs: hint of greater harm – extent: “considerable” (including respiratory, thoracic and mediastinal disorders, musculoskeletal and connective tissue disorders)
Non-serious/non-severe side effects ▪ discontinuation due to AEs: hint of lesser harm – extent: “considerable” ▪ specific AEs: indication of lesser harm – extent: “considerable” (including alopecia)	–
The underlying results are from the OAK study; the company did not consider the POPLAR study, which is also relevant, in its study pool.	
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; IC: immune cells; PD-L1: programmed cell death ligand 1; PT: Preferred Term; SOC: System Organ Class; TC: tumour cells	

In the overall consideration, there were positive and negative effects of atezolizumab in comparison with docetaxel also for patients with low PD-L1 status (TC0/1/2 and IC0/1/2).

Mostly positive effects were shown also for the patient group with low PD-L1 status. However, there was no evidence of an advantage in the outcome "overall survival". Besides, the effects in the categories of symptoms and AEs were either not visible (e.g. in SAEs) or less pronounced (e.g. diarrhoea). In view of the missing data of the POPLAR study, this did not raise general doubts about the added benefit, but the added benefit for the patient group with low PD-L1 status is non-quantifiable in the present data situation.

Hence overall, an indication of a non-quantifiable added benefit of atezolizumab in comparison with the ACT docetaxel was derived for patients with low PD-L1 status (TC0/1/2 and IC0/1/2).

2.3.5 List of included studies

Studie OAK

F. Hoffmann-La Roche. A phase III, open-label, multicenter, randomized study to investigate the efficacy and safety of atezolizumab (anti−Pd-L1 antibody) compared with docetaxel in patients with non-small cell lung caner after failure with platinum-containing chemotherapy [online]. In: EU Clinical Trials Register. [Accessed: 19.10.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-003331-30.

Hoffmann-La Roche. A study of atezolizumab compared with docetaxel in participants with locally advanced or metastatic non-small cell lung cancer who have failed platinum-containing therapy (OAK): full text view [online]. In: ClinicalTrials.gov. 02.07.2017 [Accessed: 19.10.2017]. URL: https://ClinicalTrials.gov/show/NCT02008227.

F. Hoffmann-La Roche. A phase III, open-label multicenter, randomized study to investigate the efficacy and safety of atezolizumab (anti−PD-L1 antibody) compared with docetaxel in patients with non-small cell lung cancer after failure with platinum-containing chemotherapy (OAK): study GO28915; statistical analysis plan [unpublished]. 2013.

F. Hoffmann-La Roche. A phase III, open-label multicenter, randomized study to investigate the efficacy and safety of atezolizumab (anti−PD-L1 antibody) compared with docetaxel in patients with non-small cell lung cancer after failure with platinum-containing chemotherapy (OAK): study GO28915; protocol amendment 7 [unpublished]. 2016.

Hoffmann-La Roche. A phase III, open-label multicenter, randomized study to investigate the efficacy and safety of atezolizumab (anti−PD-L1 antibody) compared with docetaxel in patients with non-small cell lung cancer after failure with platinum-containing chemotherapy (OAK): study GO28915; primary clinical study report [unpublished]. 2016.

Hoffmann-La Roche. A phase III, open-label multicenter, randomized study to investigate the efficacy and safety of atezolizumab (anti−PD-L1 antibody) compared with docetaxel in patients with non-small cell lung cancer after failure with platinum-containing chemotherapy (OAK): study GO28915; Zusatzanalysen [unpublished]. 2017.

Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, Von Pawel J et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017; 389(10066): 255-265.

Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, Von Pawel J et al. Erratum: atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK); a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017; 389(10077): e5.

Studie POPLAR

F. Hoffmann-La Roche. A phase II, open-label, multicenter, randomized study to investigate the efficacy and safety of atezolizumab (anti−Pd-L1 antibody) compared with docetaxel in patients with non-small cell lung cancer after platinum failure [online]. In: EU Clinical Trials Register. [Accessed: 19.10.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-001142-34.

Hoffmann-La Roche. A randomized phase 2 study of atezolizumab (an engineered anti−PDL1 antibody) compared with docetaxel in participants with locally advanced or metastatic non-small cell lung cancer who have failed platinum therapy: "POPLAR"; full text view [online]. In: ClinicalTrials.gov. 28.08.2017 [Accessed: 19.10.2017]. URL: https://clinicaltrials.gov/show/NCT01903993.

F. Hoffmann-La Roche. A phase II, open-label, multicenter, randomized study to investigate the efficacy and safety of atezolizumab (anti−PD-L1 antibody) compared with docetaxel in patients with non−small cell lung cancer after platinum failure: study GO28753; statistical analysis plan [unpublished]. 2015.

F. Hoffmann-La Roche. A phase II, open-label, multicenter, randomized study to investigate the efficacy and safety of atezolizumab (anti−PD-L1 antibody) compared with docetaxel in patients with non−small cell lung cancer after platinum failure: study GO28753; protocol amendment 8 [unpublished]. 2016.

Hoffmann-La Roche. A phase II, open-label, multicenter, randomized study to investigate the efficacy and safety of MPDL3280A (anti−PD-L1 antibody) compared with docetaxel in patients with non−small cell lung cancer after platinum failure: study GO28753; primary clinical study report [unpublished]. 2015.

F. Hoffmann-La Roche. A phase II, open-label, multicenter, randomized study to investigate the efficacy and safety of Atezolizumab (anti−PD-L1 antibody) compared with docetaxel in patients with non-small cell lung cancer after platinum failure: study GO28753; supplemental results report [unpublished]. 2016.

Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016; 387(10030): 1837-1846.

2.4 Research question 2: patients for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated

2.4.1 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: 13 July 2017)
- bibliographical literature search on atezolizumab (last search on 13 July 2017)
- search in trial registries for studies on atezolizumab (last search on 13 July 2017)

To check the completeness of the study pool:

- search in trial registries for studies on atezolizumab (last search on 4 October 2017)

No relevant study for research question 2 was identified from the check.

2.4.2 Results on added benefit

There were no data for the assessment of the added benefit in adult patients with locally advanced or metastatic NSCLC after prior chemotherapy (patients with activating EGFR or ALK-positive tumour mutations should also have received a therapy approved for these mutations) for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated. Hence there was no hint of an added benefit of atezolizumab in comparison with the ACT BSC. An added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

Since the company presented no data for the assessment of the added benefit of atezolizumab in adult patients for whom treatment with docetaxel, pemetrexed or nivolumab is not indicated, an added benefit of atezolizumab is not proven for these patients.

2.4.4 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of atezolizumab in comparison with the ACT is summarized in Table 22.

Table 22: Atezolizumab – probability and extent of added benefit

Research question[a]	Subindication[a]	ACT[b]	Probability and extent of added benefit
1	Adult patients with locally advanced or metastatic NSCLC after prior chemotherapy for whom treatment with docetaxel, pemetrexed or nivolumab is indicated[c]	**Docetaxel**, pemetrexed[d] 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[c]	Best supportive care[e]	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: Patients with activating EGFR mutations or ALK translocations should also have received targeted therapy before receiving atezolizumab.
d: Except in mainly squamous histology.
e: 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

This assessment regarding probability and extent of the added benefit deviates from that of the company, which derived proof of major added benefit of atezolizumab in comparison with the ACT docetaxel for adult patients with locally advanced or metastatic NSCLC after prior chemotherapy for whom treatment with docetaxel, pemetrexed or nivolumab is indicated.

According to the company, no conclusions on the added benefit can be drawn for adult patients with locally advanced or metastatic NSCLC after prior chemotherapy for whom treatment with docetaxel, pemetrexed or nivolumab or docetaxel is not indicated.

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

References for English extract

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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