Atezolizumab (NSCLC, adjuvant)

Benefit assessment according to §35a SGB V[1] (expiry of the decision)

EXTRACT

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

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

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Medical and scientific advice

- Ingo Schmidt-Wolf

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

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Jonas Goretzko
- Anna-Katharina Barnert
- Katharina Frangen
- Charlotte Guddat
- Simone Heß
- Maximilian Kind
- Petra Kohlepp
- Philip Kranz

Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
AJCC	American Joint Committee on Cancer
BICR	blinded independent central review
BSC	best supportive care
CRISP	Clinical Research platform Into molecular testing, treatment and outcome of (non-)Small cell lung carcinoma Patients
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IC	immune cells (tumour-infiltrating immune cells)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IRF	independent review facility
MRI	magnetic resonance imaging
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
PT	Preferred Term
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
TC	tumour cells
UICC	Union for International Cancer Control

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug atezolizumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 27 September 2024.

The company had already submitted a dossier for a previous benefit assessment of the drug to be assessed. The dossier was sent to IQWiG on 5 July 2022. In that procedure, by updated resolution of 17 August 2023, the G-BA limited the period of validity of the resolution to 1 October 2024.

The time limit was set because data from the prespecified final analysis of disease-free survival (DFS) in the IMpower010 study were not available at the time of the benefit assessment.

Research question

The aim of the present report is the assessment of the added benefit of atezolizumab in comparison with watchful waiting as appropriate comparator therapy (ACT) for the adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with non-small cell lung cancer (NSCLC) with a high risk of recurrence. Patients must have programmed cell death ligand 1 (PD-L1) expression on ≥ 50% of tumour cells and no epidermal growth factor receptor (EGFR)-mutant or anaplastic lymphoma kinase (ALK)-positive NSCLC. The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of atezolizumab

Therapeutic indication	**ACT**[a]
Adult patients with completely resected NSCLC at high risk of recurrence after platinum-based chemotherapy whose tumours express PD-L1 in ≥ 50% of the tumour cells and who do not have EGFR mutations or ALK-positive NSCLC; adjuvant treatment	Watchful waiting
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1	

In deviation from the G-BA, the company also named pembrolizumab as an ACT in addition to watchful waiting. The company's approach is not appropriate, but remains without consequence because the company presented data on both the G-BA's ACT and

pembrolizumab. The present benefit assessment is carried out exclusively in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive the added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

Study IMpower010

Impower110 is an ongoing, open-label, multicentre, randomized study on the comparison of atezolizumab with best supportive care (BSC). The study included adult patients with histologically or cytologically confirmed stage IB-IIIA NSCLC (classification according to the 7th edition of the Union for International Cancer Control [UICC]/the American Joint Committee on Cancer [AJCC]) after complete tumour resection independent of the PD-L1 expression and of the EGFR and ALK mutation status. According to the study protocol, tumour resection had to have taken place ≥ 28 days and ≤ 84 days before inclusion in the recruitment phase of the study. Patients had to have a good general condition corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Moreover, the patients had to be suitable for a cisplatin-based combination chemotherapy.

The IMpower010 study is divided into a recruitment phase and a subsequent randomization phase. In the recruitment phase, patients received adjuvant cisplatin-based combination chemotherapy according to investigator's choice (cisplatin in combination with vinorelbine, docetaxel, gemcitabine or pemetrexed) for up to 4 cycles. A total of 1280 patients were included in the recruitment phase of the study. The randomization phase of the study included a total of 1005 patients, randomized in a 1:1 ratio either to treatment with atezolizumab (N = 507) or BSC (N = 498).

Treatment with atezolizumab in the intervention arm was in compliance with the recommendations of the Summary of Product Characteristics (SPC). A switch of the patients from the comparator arm to treatment with atezolizumab was not provided for in the IMpower010 study.

The primary outcome of the IMpower010 study was DFS. Further secondary outcomes were outcomes in the categories of mortality, morbidity, and side effects.

In line with the company's procedure, the current 3rd data cut-off from 26 January 2024, which was prespecified for the final analysis on DFS, is used for the present benefit assessment.

Subpopulation presented by the company

In Module 4 A of the dossier, the company presented analyses for the subpopulation of patients with stage II to IIIA whose tumours have PD-L1 expression on ≥ 50% of tumour cells and no mutations in the EGFR or ALK gene or, due to the lack of determination, have an unknown mutation status of these genes. This subpopulation comprised 106 patients in the atezolizumab arm and 103 patients in the comparator arm. It is assumed that patients with stage II to IIIA disease have a high risk of recurrence.

Implementation of the ACT

The G-BA specified watchful waiting as the ACT. The examination regimen in the IMpower010 study is generally deemed to be a sufficient approximation of the ACT of watchful waiting.

Limitations of the IMpower010 study

Shifts in staging as a result of the update of the TNM classification

The inclusion of the patients in the IMpower010 study was based on the 7th edition of the TNM classification according to UICC/AJCC. In the previous procedure, the company transferred the staging to the currently valid 8th edition of the TNM classification, which led to shifts in the tumour stage for some of the tumours. According to the company, not all tumour descriptions could be precisely reassigned, which is why it was not possible to determine the exact proportion of patients affected. In the current procedure, the company subsequently submitted information showing that a maximum of 11% or 13% (discrepant data) of the patients in the relevant subpopulation can be assigned to stage IIIB according to the current 8th edition of the UICC/AJCC criteria and would therefore no longer be included in the present research question. The company did not provide any information on patients with tumour stage IB.

There is uncertainty as to whether patients with brain metastases were enrolled

To exclude cerebral metastasis, both a magnetic resonance imaging (MRI) scan and a computed tomography (CT) scan were accepted in the IMpower010 study. The sole examination by means of CT is not suitable to exclude patients with cerebral metastases with certainty. It is therefore possible that patients with brain metastases were included in the study who were not covered by the therapeutic indication.

Data on the time interval between tumour resection and adjuvant chemotherapy

Contrary to the recommendation in the S3 guideline on the prevention, diagnosis, treatment and follow-up of lung cancer, there were more than 60 days between tumour resection and adjuvant chemotherapy in approx. 35% of the patients in the presented subpopulation of the IMpower010 study. The company presented subgroup analyses for the characteristic of time interval between tumour resection and adjuvant chemotherapy for the outcomes of overall survival and DFS. No statistically significant effect modification was shown in either case. In

the group of patients in whom adjuvant chemotherapy was started ≤ 60 days after tumour resection in accordance with the guidelines, however, more pronounced effects were seen compared with the group of patients with more than 60 days between tumour resection and adjuvant chemotherapy.

Risk of bias

The risk of bias across outcomes was rated as low for the IMpower010 study. The risk of bias for the outcome of recurrence was also rated as low.

The risk of bias for the result of the outcome of overall survival is rated as high due to uncertainties in the subsequent therapies administered in the comparator arm.

The risk of bias of the results for the outcomes of serious adverse events (SAEs) and severe adverse events (AEs) as well as for the other specific AEs of pyrexia (Preferred Term [PT], AEs), skin and subcutaneous tissue disorders (System Organ Class [SOC], AEs), and infections and infestations (SOC, AEs) was rated as high in each case. For the mentioned outcomes of the category of side effects, observations are incomplete for different, potentially informative reasons due to the follow-up observation being linked to the treatment duration and a possible association between outcome and reason for treatment discontinuation.

For the specific AEs that are not serious or severe, another reason for a high risk of bias is the lack of blinding in subjective recording of outcomes. For the outcome of discontinuation due to AEs, this is the sole reason for a high risk of bias.

On the basis of the information from the IMpower010 study, no more than hints, e.g. of an added benefit, can be derived due to the limitations of the study described above.

Results

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of atezolizumab in comparison with BSC. There is a hint of an added benefit of atezolizumab in comparison with watchful waiting for the outcome of overall survival.

Morbidity

Recurrence

For the outcome of recurrence (operationalized as recurrence rate and DFS), a statistically significant difference was found between the treatment arms in favour of atezolizumab in comparison with BSC. There is a hint of an added benefit of atezolizumab in comparison with watchful waiting for this outcome.

Health-related quality of life

No data are available for the outcome of health-related quality of life. There is no hint of an added benefit of atezolizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, a statistically significant difference was found between the treatment arms to the disadvantage of atezolizumab in comparison with BSC. There is a hint of greater harm from atezolizumab in comparison with watchful waiting.

Severe AEs (CTCAE grade ≥ 3)

No statistically significant difference between the treatment arms was found for the outcome of severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3). There is no hint of greater or lesser harm from atezolizumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, a statistically significant difference was found between the treatment arms to the disadvantage of atezolizumab in comparison with BSC. There is a hint of greater harm from atezolizumab in comparison with watchful waiting.

Specific AEs

Immune-mediated SAEs and immune-mediated severe AEs

No suitable data are available for the outcomes of immune-mediated SAEs and immune-mediated severe AEs. In each case, there is no hint of greater or lesser harm from atezolizumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Pyrexia (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), infections and infestations (SOC, SAEs)

A statistically significant difference was found between the treatment arms to the disadvantage of atezolizumab in comparison with BSC for each of the outcomes of pyrexia (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), and infections and infestations (SOC, SAEs). In each case, there is a hint of greater harm from atezolizumab in comparison with watchful waiting.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug atezolizumab compared with the ACT are assessed as follows:

Overall, there are both positive and negative effects of atezolizumab in comparison with watchful waiting.

On the side of positive effects, there are hints of a non-quantifiable added benefit for the outcome of overall survival, and of a considerable added benefit for the outcome of recurrence.

On the other hand, there are hints of greater harm with different, in some cases major extent for some outcomes in the side effects category. The negative effects in the side effects do not completely call into question the positive effects in the outcomes of overall survival and recurrence. No conclusion can be drawn on the patients' symptoms and health-related quality of life, as these outcomes were not recorded in the IMpower010 study. In addition, suitable analyses of immune-mediated SAEs and immune-mediated severe AEs are lacking.

In summary, there is a hint of a minor added benefit of atezolizumab in comparison with the ACT watchful waiting for the adjuvant treatment of patients with completely resected NSCLC at high risk of recurrence after platinum-based chemotherapy whose tumours express PD-L1 in ≥ 50% of the tumour cells and who do not have EGFR mutations or ALK-positive NSCLC.

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

[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].

Table 3: Atezolizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with completely resected NSCLC at high risk of recurrence after platinum-based chemotherapy whose tumours express PD-L1 in ≥ 50% of the tumour cells and who do not have EGFR mutations or ALK-positive NSCLC; adjuvant treatment	Watchful waiting	Hint of minor added benefit
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1		

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

I 2 Research question

The aim of the present report is the assessment of the added benefit of atezolizumab in comparison with watchful waiting as ACT for the adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence. Patients must have PD-L1 expression on ≥ 50% of tumour cells and no EGFR-mutant or ALK-positive NSCLC.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of atezolizumab

Therapeutic indication	**ACT[a]**
Adult patients with completely resected NSCLC at high risk of recurrence after platinum-based chemotherapy whose tumours express PD-L1 in ≥ 50% of the tumour cells and who do not have EGFR mutations or ALK-positive NSCLC; adjuvant treatment	Watchful waiting
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1	

In deviation from the G-BA, the company also named pembrolizumab as an ACT in addition to watchful waiting. The company's approach is not appropriate, but remains without consequence because the company presented data on both the G-BA's ACT and pembrolizumab (see Chapter I 3). The present benefit assessment is carried out exclusively in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive the added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on atezolizumab (status: 13 August 2024)
- bibliographical literature search on atezolizumab (last search on 12 August 2024)
- search in trial registries/trial results databases for studies on atezolizumab (last search on 19 August 2024)
- search on the G-BA website for atezolizumab (last search on 13 August 2024)
- bibliographical literature search on the ACT (last search on 19 August 2024)
- search in trial registries/trial results databases for studies on the ACT (last search on 19 August 2024)
- search on the G-BA website for the ACT (last search on 13 August 2024)

To check the completeness of the study pool:

- search in trial registries for studies on atezolizumab (last search on 15 October 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

As described in Chapter I 2, the company also named pembrolizumab as part of the ACT. The company identified the RCT KEYNOTE-091 [3] as part of its information retrieval for pembrolizumab. It used this study for an indirect comparison of atezolizumab (RCT IMpower010, see Section I 3.1) versus pembrolizumab. The company's search for RCTs with pembrolizumab was not checked for completeness, as pembrolizumab is not part of the ACT of the G-BA (see Chapter I 2). The KEYNOTE-091 study is therefore not relevant for the present research question, and the indirect comparison is not considered further.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

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

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
GO29527 (IMpower010[d])	Yes	Yes	No	Yes [4,5]	Yes [6,7]	Yes [8-14]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

I 3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: atezolizumab vs. BSC (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
IMpower010	RCT, open-label, parallel	Adult patients ▪ with histologically or cytologically confirmed stage IB–IIIA NSCLC[b] ▪ after complete tumour resection[c] and subsequent adjuvant cisplatin-based chemotherapy[d, e] ▪ ECOG PS 0 or 1	Atezolizumab (N = 507) BSC (N = 498) Relevant subpopulation thereof[f]: atezolizumab (n = 106) BSC (n = 103)	▪ Screening: up to 28 days ▪ Treatment: atezolizumab for 16 cycles or until disease progression, unacceptable toxicity, or patient's or investigator's decision to discontinue the study ▪ Observation[g]: outcome-specific, at most until death, loss to follow-up, withdrawal of consent, or end of study	204 study centres in: Australia, Canada, China, France, Germany, Hong Kong, Hungary, Israel, Italy, Japan, Netherlands, Poland, Portugal, Romania, Russia, South Korea, Spain, Taiwan, Ukraine, United Kingdom, United States 10/2015–ongoing Data cut-offs: ▪ 21 January 2021[h] ▪ 18 April 2022[i] ▪ 26 January 2024[j]	Primary: disease-free survival Secondary: overall survival, morbidity, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: atezolizumab vs. BSC (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Staging based on UICC/AJCC classification, edition 7.
c. Enrolment took place ≥ 28 days and ≤ 84 days after tumour resection (according to study protocol version 1 [1 April 2015] ≥ 42 days and ≤ 84 days). At enrolment, patients had to be adequately recovered from surgery.
d. The study is divided into a recruitment phase and a randomization phase including follow-up observation (see body of text below). Patients included in the study received adjuvant cisplatin-based chemotherapy during the recruitment phase.
e. Patients received up to 4 cycles of 1 of 4 cisplatin-based chemotherapy regimens (cisplatin in combination with vinorelbine, docetaxel, gemcitabine or pemetrexed) based on investigator choice.
f. Patients with stage II to IIIA NSCLC, PD-L1 expression on ≥ 50% of tumour cells, without EGFR mutation and without ALK fusion.
g. Outcome-specific information is provided in Table 8.
h. Interim analysis of disease-free survival after 193 events (planned after about 190 events) in the population of patients with stage II–IIIA NSCLC with PD-L1 expression on ≥ 1% of tumour cells.
i. Interim analysis of overall survival after 251 events (planned after about 254 events) in the total population.
j. Final analysis of disease-free survival after 240 events (planned after about 237 events) in the population of patients with stage II–IIIA NSCLC with PD-L1 expression on ≥ 1% of tumour cells, and interim analysis of overall survival after 316 events in the total population.

AE: adverse event; AJCC: American Joint Committee on Cancer; ALK: anaplastic lymphoma kinase; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; n: relevant subpopulation; N: number of randomized patients; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; UICC: Union for International Cancer Control

Table 7: Characteristics of the intervention – RCT, direct comparison: atezolizumab vs. BSC (multipage table)

Study	Intervention	Comparison
IMpower010	Atezolizumab 1200 mg on Day 1 of a 21-day cycle, IV[a, b] (for a maximum of 16 cycles)	BSC[b]
	Dose adjustment: ▪ no dose adjustment allowed; interruption allowed for up to 105 days in case of side effects[c]	
	Pretreatment ▪ complete surgical resection of the NSCLC ≥ 28 days and ≤ 84 days[d] before enrolment ▪ adjuvant cisplatin-based combination chemotherapy based on investigator choice for up to 4 cycles **Disallowed pretreatment** ▪ prior systemic chemotherapy[e] ▪ hormonal cancer therapy or radiation therapy within 5 years before enrolment ▪ other investigational products within 28 days prior to enrolment ▪ CD137 agonists or immune checkpoint inhibitors, anti-PD-1 and anti-PD-L1 therapeutic antibodies ▪ antibiotics within 14 days prior to randomization ▪ systemic immunostimulatory agents within 4 weeks[f] prior to randomization ▪ systemic corticosteroids or other immunosuppressants within 14 days prior to randomization[g] **Premedication** ▪ antihistamines (from Cycle 2) **Allowed concomitant treatment** ▪ corticosteroids (≤ 10 mg/day prednisone or equivalent) for chronic obstructive pulmonary disease ▪ low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency **Disallowed concomitant treatment** ▪ other cancer therapies including chemotherapy, immunotherapy, radiotherapy, investigational products, or herbal therapy ▪ steroids to premedicate patients for whom CT contrast agents are contraindicated	

a. The first atezolizumab dose was administered over 60 (± 15) minutes. If no infusion related reactions occurred, subsequent doses were administered over 30 (± 10) minutes. If an infusion related reaction occurred, the subsequent dose had to be administered over 60 (± 15) minutes.
b. On Day 1 of each 21-day cycle, in addition to the study treatment administration, patients in the intervention arm had a visit with a complete assessment of clinical parameters (including blood tests). In the comparator arm, patients in Cycles 1, 3, 5, 7, 9, 11, 13 and 15 had a visit analogous to the intervention arm. In Cycles 2, 4, 6, 8, 10, 12, 14 and 16, visits in the comparator arm could be either a formal clinic visit, or a telephone visit without complete recording of all clinical parameters.
c. An interruption of more than 105 days was permitted to taper off corticosteroids.
d. According to study protocol version 1 [1 April 2015] ≥ 42 days and ≤ 84 days.
e. Except curative treatment for early-stage cancer, provided that the last dose received was > 5 years prior to enrolment, and low-dose chemotherapy for non-malignant conditions.
f. Or 5 half-lives, whichever is longer (before study protocol version 4 [5 October 2015] within 6 weeks or 5 half-lives).
g. Acute, low-dose immunosuppressants and corticosteroids (≤ 10 mg/day prednisone or equivalent) for chronic obstructive pulmonary disease, mineralocorticoids for orthostatic hypotension, or low-dose corticosteroids for adrenal insufficiency were allowed.

Table 7: Characteristics of the intervention – RCT, direct comparison: atezolizumab vs. BSC (multipage table)

Study	Intervention	Comparison
BSC: best supportive care; CD137: cluster of differentiation 137; CT: computed tomography; IV: intravenous; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial		

Design of the IMpower010 study

Impower110 is an ongoing, open-label, multicentre, randomized study on the comparison of atezolizumab with BSC. The study included adult patients with histologically or cytologically confirmed stage IB-IIIA NSCLC (classification according to the 7th edition of the UICC/the AJCC) after complete tumour resection independent of the PD-L1 expression and of the EGFR and ALK mutation status. According to the study protocol, tumour resection had to have taken place ≥ 28 days and ≤ 84 days before inclusion in the recruitment phase of the study (see following section). Patients had to have a good general condition corresponding to an ECOG PS of 0 or 1. Moreover, the patients had to be suitable for a cisplatin-based combination chemotherapy.

At study inclusion, PD-L1 expression of the tumour tissue was determined by immunohistochemical tests by a central laboratory. The Ventana PD-L1 (SP142) assay (hereinafter referred to as SP142 assay), the Ventana PD-L1 (SP263) assay (hereinafter referred to as SP263 assay) and the PD-L1 IHC 22C3 assay were used to determine the PD-L1 expression.

The IMpower010 study is divided into a recruitment phase and a subsequent randomization phase. In the recruitment phase, patients received adjuvant cisplatin-based combination chemotherapy according to investigator's choice (cisplatin in combination with vinorelbine, docetaxel, gemcitabine or pemetrexed) for up to 4 cycles. A total of 1280 patients were included in the recruitment phase of the study. Following adjuvant cisplatin-based combination chemotherapy, patients were rescreened to assess their suitability for further participation in the study. Randomization took place within 3 to 8 weeks after the last dose of the platinum-based chemotherapy.

The randomization phase of the study included a total of 1005 patients, randomized in a 1:1 ratio either to treatment with atezolizumab (N = 507) or BSC (N = 498). Randomization was stratified by sex (male versus female), histology (squamous versus non-squamous), disease stage (IB versus II versus IIIA) and PD-L1 expression in tumour tissue, determined by immunohistochemistry using the SP142 assay for tumour cells (TC) and tumour-infiltrating immune cells ([IC]; TC2/3 and any IC versus TC0/1 and IC2/3 versus TC0/1 and IC0/1).

Treatment with atezolizumab in the intervention arm was in compliance with the specifications of the SPC [15]. A switch of the patients from the comparator arm to treatment with atezolizumab was not provided for in the IMpower010 study.

The primary outcome of the IMpower010 study was disease-free survival (DFS). Further secondary outcomes were outcomes in the categories of mortality, morbidity, and side effects.

Data cut-offs

Three data cut-offs are currently available for the IMpower010 study:

- 21 January 2021 (prespecified interim analysis on DFS, planned after approx. 190 events in patients with stage II to IIIA with PD-L1 expression ≥ 1%)
- 18 April 2022 (prespecified interim analysis on overall survival, planned after approx. 254 events in the total study population)
- 26 January 2024 (prespecified final analysis on DFS, planned after approx. 237 events in patients with stage II to IIIA with PD-L1 expression ≥ 1%)

The current 3rd data cut-off dated 26 January 2024 is relevant for the present benefit assessment. Analogously to the company's approach, this is used for the benefit assessment and is presented below. According to the study protocol, 2 further interim analyses on overall survival are planned during the course of the study. The study ends with the prespecified final analysis of overall survival after approx. 564 events in the total population.

Subpopulation presented by the company

In Module 4 A of the dossier, the company presented analyses for the subpopulation of patients with stage II to IIIA whose tumours have PD-L1 expression on ≥ 50% of tumour cells (determined using the SP263 assay) and no mutations in the EGFR or ALK gene or, due to the lack of determination, have an unknown mutation status of these genes. This subpopulation comprised 106 patients in the atezolizumab arm and 103 patients in the comparator arm. It is assumed that patients with stage II to IIIA disease have a high risk of recurrence.

Implementation of the ACT

The G-BA specified watchful waiting as the ACT. The IMpower010 study used BSC as comparator therapy. The study was not designed for a comparison with watchful waiting, but is in principle suitable for such a comparison. The examinations carried out in the study do not fully correspond to the recommendations of the currently valid guidelines [16,17]; however, the examination regimen in the IMpower010 study is in principle considered to be a sufficient approximation of the ACT of watchful waiting.

Limitations of the IMpower010 study

Shifts in staging as a result of the update of the TNM classification

The inclusion of the patients in the IMpower010 study was based on the 7th edition of the TNM classification according to UICC/AJCC. In the previous procedure, the company transferred the staging to the currently valid 8th edition of the TNM classification, which led to shifts in the tumour stage for some of the tumours. In the previous procedure, the proportion of patients who would no longer be covered by the research question due to the current TNM classification was estimated at a maximum of 19.1% on the basis of the data presented, and comprised patients with stage Ib and IIIB according to the 8th edition. However, according to the company, not all tumour descriptions could be precisely reassigned, which is why it was not possible to determine the exact proportion of patients affected [13].

In the current procedure, the company presented information on how many of the patients in the relevant subpopulation can be assigned to stage IIIB according to the current 8th edition of the UICC/AJCC criteria and would therefore no longer be included in the present research question. It did not provide any information on patients with stage IB. It distinguished between patients who can be safely assigned to stage IIIB (8th edition) and those who cannot be assigned with certainty due to a lack of information. The information provided in the dossier is discrepant. In Module 4, the company stated that a maximum of 24 patients of the relevant subpopulation (corresponding to 11%) can be assigned to stage IIIB. It referred to a tabular overview in Module 4 Appendix 4-G2, but this table shows that a maximum of 27 patients can be classified as stage IIIB (corresponding to 13%). Of these 27 patients, 18 were definitely in stage IIIB and 9 were potentially in stage IIIB.

The company did not present any sensitivity analyses on the patient-relevant outcomes that do not include these patients.

There is uncertainty as to whether patients with brain metastases were enrolled

To exclude cerebral metastasis, both a MRI scan and a CT scan were accepted in the IMpower010 study. The sole examination by means of CT is not suitable to exclude patients with cerebral metastases with certainty. It is therefore possible that patients with brain metastases were included in the study who were not covered by the therapeutic indication. The company did not present information on the use of CT and MRI scans of the cranium. In the commenting procedure on A22-67, the company pointed out that all patients received brain scans before inclusion in the IMpower010 study, but that it had no specific information on the type of scans used [18]. The uncertainty regarding the inclusion of patients with brain metastases therefore remains.

Data on the time interval between tumour resection and adjuvant chemotherapy

It was noted in the previous procedure that, contrary to the recommendation in the S3 guideline on the prevention, diagnosis, treatment and follow-up of lung cancer [16], there were more than 60 days between tumour resection and adjuvant chemotherapy in approx. 35% of the patients in the presented subpopulation of the IMpower010 study. In the current dossier, the company presented subgroup analyses for the 3rd data cut-off from 26 January 2024. These subgroup analyses for the outcomes on side effects are missing.

For each of the outcomes of overall survival and DFS, there was no statistically significant effect modification by the characteristic of time interval between tumour resection and adjuvant chemotherapy also in the present data cut-off. In the group of patients in whom adjuvant chemotherapy was started ≤ 60 days after tumour resection in accordance with the guidelines, however, more pronounced effects were seen compared with the group of patients with more than 60 days between tumour resection and adjuvant chemotherapy. Furthermore, in the previous procedure, the company had presented analyses from the Clinical Research platform Into molecular testing, treatment and outcome of (non-)Small cell lung carcinoma Patients (CRISP) registry, which showed that the time interval between surgery and chemotherapy of 60 days is also sometimes exceeded in the German health care context [18]. However, with 14%, this is much less often the case than in the IMpower010 study with approx. 35%.

Summary

The uncertainties described above, in particular regarding the proportion of patients in the presented subpopulation who are not covered by the research question of the present benefit assessment, limit the certainty of conclusions. Thus, based on the results of the IMpower010 study, no more than hints, e.g. of an added benefit, can be derived (see also Section I 4.2).

Planned duration of follow-up observation

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

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

Study **Outcome category** **Outcome**	**Planned follow-up observation**
IMpower010	
Mortality	
Overall survival	Until death, loss to follow-up, withdrawal of consent, or end of study
Morbidity	
Recurrence[a]	Until the occurrence of a recurrence, death, loss to follow-up, withdrawal of consent, or end of study
Health-related quality of life	Outcome not recorded
Side effects	
SAEs and AESIs	Up to 90 days[b] after the last dose of the study medication or the last examination (comparator arm) or initiation of new antineoplastic treatment
Further AEs	Up to 30 days after the last dose of the study medication or the last examination (comparator arm) or initiation of new antineoplastic treatment

a. Presented based on the recurrence rate and disease-free survival; includes the events of local recurrence, regional recurrence, remote recurrence, new primary NSCLC, as well as death without recurrence.
b. Before version 4 of the study protocol dated 5 October 2015, 30 days after the last dose of the study medication or initiation of new antineoplastic treatment.

AE: adverse event; AESI: adverse event of special interest; BSC: best supportive care; NSCLC: non-small cell lung cancer; RCT: randomized controlled trial; SAE: serious adverse event

The observation periods for the outcomes in the outcome category of side effects are systematically shortened because they were only recorded for the time period of treatment with the study medication or the last examination in the comparator arm (plus 30 or 90 days). Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

Patient characteristics

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: atezolizumab vs. BSC (multipage table)

Study **Characteristic** **Category**	**Atezolizumab** **N[a] = 106**	**BSC** **N[a] = 103**
IMpower010		
Age [years], mean (SD)	61 (9)	61 (9)
Sex [F/M], %	21/79	29/71
Family origin, n (%)		
Asian	31 (29)	24 (23)
Black or African American	1 (< 1)	0 (0)
Native Hawaiian or other Pacific Islander	1 (< 1)	0 (0)
White	71 (67)	77 (75)
Unknown	2 (2)	2 (2)
Smoking status, n (%)		
Never smoker	11 (10)	10 (10)
Active	16 (15)	21 (20)
Former	79 (75)	72 (70)
ECOG PS, n (%)		
0	66 (62)	53 (51)
1	40 (38)	49 (48)
2	0 (0)	1 (< 1)[b]
Disease stage[c], n (%)		
IIA	31 (29)	33 (32)
IIB	27 (25)	15 (15)
IIIA	48 (45)	55 (53)
Histology, n (%)		
Squamous	47 (44)	45 (44)
Non-squamous	59 (56)	58 (56)
EGFR mutation status		
No	57 (54)	61 (59)
Unknown	49 (46)	42 (41)
ALK mutation status		
No	56 (53)	55 (53)
Unknown	50 (47)	48 (47)
Time between first diagnosis and first treatment after randomization [months], mean (SD)	5.6 (1.1)	5.4 (1.3)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: atezolizumab vs. BSC (multipage table)

Study **Characteristic** **Category**	**Atezolizumab** **N[a] = 106**	**BSC** **N[a] = 103**
Type of resection, n (%)		
Lobectomy	76 (72)	74 (72)
Sleeve lobectomy	2 (2)	1 (< 1)
Bilobectomy	7 (7)	7 (7)
Pneumonectomy	20 (19)	20 (19)
Other	1 (< 1)	1 (< 1)
Time between tumour resection and start of adjuvant chemotherapy [days], median [min; max]	55 [31; 121]	51 [24; 91]
≤ 60 days, n (%)	68 (64)	68 (66)
> 60 days, n (%)	38 (36)	35 (34)
Number of chemotherapy cycles, n (%)		
1 cycle	0 (0)	7 (7)
2 cycles	5 (5)	6 (6)
3 cycles	9 (9)	6 (6)
4 cycles	92 (87)	84 (82)
Treatment discontinuation by the 3rd data cut-off (26 January 2024), n (%)[d]	27 (25[e])	27 (26[e])
Study discontinuation by the 3rd data cut-off (26 January 2024), n (%)[f]	34 (32)	51 (50)

a. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. The condition of one patient deteriorated during the transition from the recruitment phase to the randomization phase.
c. Staging based on UICC/AJCC classification, edition 7.
d. Common reasons for treatment discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients): AEs (19% vs. < 1%), withdrawal by patient (5% vs. 2%), disease relapse (2% vs. 22%). In addition, 2% vs. 2% of randomized patients never started treatment, and 73% vs. 72% of patients completed treatment as planned.
e. Institute's calculation.
f. A common reason for study discontinuation in the intervention arm vs. control arm was the following (percentages based on randomized patients): withdrawal by patient (11% vs. 8%). The data additionally include patients who died during the course of the study (intervention arm: 21% vs. control arm: 40%).

AE: adverse event; AJCC: American Joint Committee on Cancer; ALK: anaplastic lymphoma kinase; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; F: female; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients in the approval population; RCT: randomized controlled trial; SD: standard deviation; UICC: Union for International Cancer Control

The characteristics of the patients are largely balanced between both treatment arms of the IMpower010 study. The mean patient age was 61 years; most of them were male (79% versus

71%) and White (67% versus 75%). 62% of the patients in the intervention arm had an ECOG PS of 0, whereas this percentage was slightly lower (51%) in the comparator arm.

Tumour staging in the study was based on the 7th edition of the UICC/AJCC classification, and most patients were enrolled with stage IIIA (45% versus 53%). For 64% versus 66% of patients, the time between surgery and the first dose of adjuvant chemotherapy was ≤ 60 days.

Treatment with atezolizumab in the intervention arm and BSC in the comparator arm was discontinued with approximately the same frequency (25% versus 26%). The main reasons for discontinuation of treatment were AEs in the intervention arm, and disease relapse in the comparator arm.

Course of the study

Table 10 shows the patient treatment duration and the mean/median observation period for individual outcomes.

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

Study **Duration of the study phase** **Outcome category/outcome**	**Atezolizumab** **N = 106**	**BSC** **N = 103**
IMpower010		
Treatment duration [months]	ND	ND
Observation period [months]		
Overall survival[a]		
Median [Q1; Q3]	68.9 [57.4; 76.2]	65.2 [29.8; 74.3]
Mean (SD)	62.8 (20.5)	53.9 (25.6)
Morbidity (recurrence)	ND	ND
Health-related quality of life	Outcome not recorded	
Side effects		
AEs and severe AEs[b, c]		
Median [Q1; Q3]	11.3 [11.1; 11.7]	12.0 [11.1; 12.3]
Mean (SD)	9.9 (3.6)	10.8 (3.3)
SAEs and AESIs[b, d]		
Median [Q1; Q3]	13.3 [13.0; 13.6]	14.0 [13.1; 14.2]
Mean (SD)	11.8 (3.7)	12.5 (3.6)

a. Calculated as time from randomization to the time point of the 3rd data cut-off, death, loss to follow-up, withdrawal of consent or study discontinuation.
b. Data based on N = 104 patients (intervention) vs. N = 101 patients (control).
c. Calculated as time since start of treatment until the time point of the 3rd data cut-off, death, loss to follow-up, withdrawal of consent, study discontinuation, until 30 days after the last dose of the study medication or until initiation of a subsequent anticancer therapy.
d. Calculated as time since start of treatment until the time point of the 3rd data cut-off, death, loss to follow-up, withdrawal of consent, study discontinuation, until 90 days after the last dose of the study medication or until initiation of a subsequent anticancer therapy.

AE: adverse event; AESI: adverse events of special interest; BSC: best supportive care; N: number of analysed patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation

There is no information on the treatment duration. The median observation period for the outcome of overall survival was slightly longer in the intervention arm than in the comparator arm. The median observation periods for the side effect outcomes are comparable between the treatment arms, but markedly shorter compared with overall survival.

Subsequent therapies

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies referring to patients with recurrence – RCT, direct comparison: atezolizumab vs. BSC (multipage table)

Study (data cut-off) **Drug**	**Patients with subsequent therapy, n (%)**	
	Atezolizumab N = 106	**BSC N = 103**
IMpower010 (data cut-off: 26 January 2024)		
Patients with recurrence	28 (26.4)	47 (45.6)
Patients with radiation therapy, n (%[a])	14 (50.0)	24 (51.1)
Brain	2 (7.1)	12 (25.5)
Lymph nodes	6 (21.4)	5 (10.6)
Lung	5 (17.9)	5 (10.6)
Bones	2 (7.1)	4 (8.5)
Other	0 (0)	1 (2.1)
Patients with surgery, n (%[a])	5 (17.9)	10 (21.3)
Brain	0 (0)	6 (12.8)
Chest wall	1 (3.6)	0 (0)
Lung	3 (10.7)	3 (6.4)
Lymph nodes	0 (0)	1 (2.1)
Other	1 (3.6)	1 (2.1)
Patients with at least one subsequent systemic therapy n (%)[a]	21 (75.0)	29 (61.7)
Immune checkpoint inhibitor[b]		
Atezolizumab	0 (0)	3 (6.4)
Durvalumab	1 (3.6)	1 (2.1)
Ipilimumab	0 (0)	2 (4.3)
Nivolumab	0 (0)	2 (4.3)
Pembrolizumab	4 (14.3)	15 (31.9)
Carboplatin	13 (46.4)	11 (23.4)
Docetaxel	4 (14.3)	6 (12.8)
Cisplatin	4 (14.3)	6 (12.8)
Gemcitabine	5 (17.9)	4 (8.5)
Pemetrexed	5 (17.9)	5 (10.6)
Paclitaxel	4 (14.3)	3 (6.4)
Ramucirumab	2 (7.1)	1 (2.1)
Etoposide	3 (10.7)	1 (2.1)
Gimeracil/oteracil potassium/tegafur	2 (7.1)	1 (2.1)
Vinorelbine	2 (7.1)	0 (0)
Vinorelbine tartrate	1 (3.6)	1 (2.1)
Afatinib dimaleate	1 (3.6)	1 (2.1)
Bevacizumab	0 (0)	3 (6.4)

Table 11: Information on subsequent antineoplastic therapies referring to patients with recurrence – RCT, direct comparison: atezolizumab vs. BSC (multipage table)

Study (data cut-off) Drug	Patients with subsequent therapy, n (%)	
	Atezolizumab N = 106	BSC N = 103
Crizotinib	1 (3.6)	0 (0)
Epacadostat	0 (0)	1 (2.1)
Gemcitabine hydrochloride	0 (0)	2 (4.3)
Nintedanib	0 (0)	1 (2.1)
Osimertinib	0 (0)	2 (4.3)
Paclitaxel albumin	0 (0)	2 (4.3)
B-RAF serine threonine kinase (BRAF) inhibitor	0 (0)	1 (2.1)
Miriplatin	0 (0)	1 (2.1)
Selpercatinib	1 (3.6)	0 (0)

a. Institute's calculation; referring to patients with recurrence.
b. At the data cut-off on 26 January 2024, a maximum of 5 (17.9%) of the 28 patients with recurrence in the intervention arm and a maximum of 23 (48.9%) of the 47 patients with recurrence in the comparator arm received an immune checkpoint inhibitor as part of the subsequent therapy.

BSC: best supportive care; n: number of patients with subsequent therapy; N: number of randomized patients in the approval population; RCT: randomized controlled trial

The guideline recommendations for the advanced therapy stage of NSCLC are decisive for the assessment of the administered subsequent therapies in the IMpower010 study. According to the S3 guideline on the prevention, diagnosis, treatment and follow-up of lung cancer and the guideline of the German Society for Haematology and Medical Oncology, patients with advanced or metastatic NSCLC who have no treatable mutations and no contraindication to immune checkpoint inhibitors (in the present therapeutic indication primarily PD-1/PD-L1 inhibitors) should receive systemic therapy with an immune checkpoint inhibitor or a combination of immune checkpoint inhibitor and chemotherapy in the first line [16,17]. These recommendations are based on advantages in overall survival through the use of immune checkpoint inhibitors (also in combination with chemotherapy) compared with chemotherapy [16,17]. As already addressed in the previous benefit assessment [13,14], the subsequent therapies used in the IMpower010 study do not adequately reflect the current standard of care after recurrence. This is explained in more detail below.

The company presented data on subsequent antineoplastic therapies for the relevant subpopulation from the current data cut-off of 26 January 2024. These include radiation therapy, surgery and systemic therapy. In relation to the number of patients with recurrence, it can be seen that the proportions of local procedures, such as radiation therapy (approx. 50%) and surgery (approx. 20%), are comparable between the arms. The proportion of systemic therapies as subsequent therapies, on the other hand, was higher in the intervention

arm (75%) than in the comparator arm (62%). Hence, around 40% of patients with recurrence in the comparator arm, and around 25% in the intervention arm received no subsequent systemic therapy. This proportion did not change notably compared with the previous 2nd data cut-off. A maximum of 23 (49%) of the 47 patients with recurrence in the comparator arm received an immune checkpoint inhibitor. Particularly in view of the higher proportion of remote recurrences in patients with recurrence in the comparator arm (39% versus 60%), it remains unclear why the proportion of subsequent systemic therapies is lower in the comparator arm than in the intervention arm. The company did not provide any information on how the local procedures and systemic therapies are distributed among the types of recurrence.

Although it is possible that (as described by the company in the previous procedure) local treatment of the metastases by means of surgery or radiation therapy is initially indicated also for patients with individual distant metastases, it can be assumed that from a certain point onwards in the further progressive course of the disease, subsequent systemic therapy is indicated – with the guideline-compliant use of checkpoint inhibitors in the first line. The only low proportion of immune checkpoint inhibitors used, compared with the German health care context, may be due to the different country-specific availability of the drugs in the respective study centres.

The company also stated that the mutation status may also change if a recurrence occurs. The use of molecularly targeted therapies may therefore also be indicated. In the dossier, the company provided information on the first subsequent systemic therapy administered. According to this information, 5% of the patients with subsequent systemic therapy in the intervention arm and 14% of the patients in the comparator arm received targeted therapy as first subsequent systemic therapy. Even taking into account the proportion of patients who received a targeted therapy as part of the first subsequent systemic therapy, approximately 50% of patients with recurrence did not receive an immune checkpoint inhibitor as part of the first subsequent therapy. The use of targeted therapies in recurrence therefore does not resolve the uncertainties relating to the low proportion of immune checkpoint inhibitors in the comparator arm. In accordance with the guideline recommendations, it can therefore be assumed that subsequent therapy using an immune checkpoint inhibitor would have been indicated for almost all patients with recurrence, especially in the presence of distant metastases, in the comparator arm of the IMpower010 study subpopulation presented by the company.

On the basis of the available data, it must therefore be assumed overall that the systemic therapy of the patients after recurrence in the comparator arm was insufficient. This is of particular importance in the present research question, the adjuvant treatment of NSCLC: Treatment with an immune checkpoint inhibitor in advanced or metastatic disease is

associated with a clear survival advantage [17]. The research question to be answered is therefore whether overall survival is improved if patients who are considered disease-free receive adjuvant therapy with an immune checkpoint inhibitor, instead of this therapy only being used after the occurrence of a manifest recurrence, as has been the case up to now.

Overall, the described deficiencies in the subsequent therapies administered in the IMpower010 study are still considered to be serious. The important deficiencies with regard to the subsequent therapies used are taken into account for the outcome of overall survival when assessing the risk of bias and determining the extent (see Section I 4.2).

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: atezolizumab vs. BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
IMpower010	Yes	Yes	No	No	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the IMpower010 study. Limitations resulting from the open-label study design are described in Section I 4.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company justified the transferability of the study results to the German health care context by comparing the characteristics of the patients in the IMpower010 study with data from the German CRISP cancer registry and the lung cancer tumour registry. The company pointed out that more than 70% of the patients in the relevant subpopulation were Caucasian and, with a mean age of 61 years, were only slightly younger than the patients from the registries (approx. 67 and 63 years). It added that the sex distribution, the proportion of never-smokers and the distribution of histology (squamous versus non-squamous) were also comparable to the registry data, and that the percentage distribution regarding the surgical procedure in the approval population was comparable to data from the CRISP registry. According to the company, an exact comparison of the percentage distribution of the stages with the data from the CRISP registry was not possible due to the shifts between UICC 7 and

UICC 8. The IMpower010 study complied with the recommendations of the German S3 guideline with regard to the inclusion of patients with ECOG 0 or 1, the proportion of patients who received 4 cycles of cisplatin-based chemotherapy, and the use of vinorelbine as the most common combination partner, the company added. According to the company, the period from surgery to the start of adjuvant cisplatin-based chemotherapy corresponded in most cases (65%) to the recommendations of the S3 guidelines, which recommends adjuvant chemotherapy to start within 60 days of resection. The proportion of patients in whom adjuvant cisplatin-based chemotherapy was administered more than 60 days after surgery was also comparable between the arms, which is why the company did not assume that this would have unilaterally influenced or favoured the effect of atezolizumab. There was also no effect modification for this characteristic (≤ 60 days versus > 60 days) in either overall survival or DFS, the company added.

In summary, the company deemed the patients in the IMpower010 study to correspond to the German health care context both with regard to general patient characteristics and with regard to disease-specific criteria.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also Section I 3.2.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - recurrence
- Health-related quality of life
- Side effects
  - SAEs
  - severe AEs (operationalized as CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - immune-mediated SAEs
  - immune-mediated severe AEs (CTCAE grade ≥ 3)
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4).

Table 13 shows the outcomes for which data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: atezolizumab vs. BSC

Study	Outcomes							
	Overall survival	Recurrence[a]	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-mediated SAEs and severe AEs	Other specific AEs[c]
IMpower010	Yes	Yes	No[d]	Yes	Yes	Yes	No[e]	Yes

a. Presented based on the recurrence rate and disease-free survival; includes the events of local recurrence, regional recurrence, remote recurrence, new primary lung cancer, as well as death without recurrence.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The following events (MedDRA coding) were considered: pyrexia (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), and infections and infestations (SOC, SAEs).
d. Outcome not recorded.
e. No suitable data available; see body of text for reasons.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Overall survival

The overall survival of patients in the present therapeutic indication is composed of a phase of DFS until recurrence and the subsequent stage of advanced and/or metastatic NSCLC.

An observed effect in the outcome of overall survival is not only influenced by the initial study treatment, but also by the subsequent antineoplastic therapies used after disease progression or recurrence [19-21]. In order for an observed effect in the outcome of overall survival to be interpreted meaningfully, adequate guideline-compliant subsequent treatment of patients after progression or recurrence of the disease is therefore necessary, especially in the adjuvant therapy situation.

As described in Section I 3.2, the IMpower010 study is considered to have serious shortcomings with regard to the subsequent therapies used in the comparator arm. Due to the size of the effect in the outcome of overall survival, it is nevertheless considered to be interpretable to a limited extent, even if the extent is considered as non-quantifiable due to the uncertainties described.

Recurrence

The outcome of recurrence is a composite outcome and comprises the components of death (without previous recurrence), local recurrence, regional recurrence, remote recurrence, and

new primary lung cancer. For the outcome of recurrence, the results of the operationalizations of recurrence rate (occurrence of an event) and disease-free survival (time to event) are presented. The patients considered in the present stage of the disease are a group of patients who were treated with a curative treatment approach. The occurrence of a recurrence in this situation means that the attempt at cure by the curative treatment approach was not successful.

In the unblinded IMpower010 study, disease-free survival was assessed by the investigators. In the course of the study, the option of a retrospective blinded independent central review (BICR) by an independent review facility (IRF) was introduced with study protocol version 9. According to the company, this central review was based on imaging data and other clinical data and was available for around 94% of patients in the relevant subpopulation at the current data cut-off on 26 January 2024. However, the analysis on DFS according to BICR presented by the company did not include a list of the individual qualifying events. Besides, not all patients were included in this analysis, which further limits the interpretability of this analysis. Based on the available analyses, however, no relevant differences for DFS were found between the assessment by the investigators and the BICR. Therefore, the prespecified analyses by the investigator are used for the present benefit assessment. The BICR analyses are not presented.

Notes on the immune-mediated AEs

The company did not present a summary analysis of immune-mediated events for immune-mediated AEs (AEs, serious AEs, severe AEs). Instead, in Module 4 A, it only presented results for individual categories of immune-mediated AEs within the framework of the analyses on the specific AEs of special interest. The analyses presented by the company are not suitable to provide a comprehensive reflection of the immune-mediated AEs. However, events that can be classified as immune-mediated AEs are captured via the analyses of AEs (overall rates and specific AEs; see results in Section I 4.3 and I Appendix C of the full dossier assessment).

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: atezolizumab vs. BSC

Study	Study level	Outcomes							
		Overall survival	Recurrence[a]	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-mediated SAEs and severe AEs	Other specific AEs[c]
IMpower010	L	H[d]	L	–[e]	H[f]	H[f]	H[g]	–[h]	H[f, g]

a. Presented based on the recurrence rate and disease-free survival; includes the events of local recurrence, regional recurrence, remote recurrence, new primary lung cancer, as well as death without recurrence.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The following events (MedDRA coding) were considered: pyrexia (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), and infections and infestations (SOC, SAEs).
d. Uncertainties regarding the use of adequate subsequent therapies (see Section I 4.1).
e. Outcome not recorded.
f. Patients with incomplete observation due to clearly different reasons for treatment discontinuation.
g. Lack of blinding in the case of subjective decision to discontinue, or subjective recording of outcomes in the case of other specific AEs at AE level.
h. No suitable data available; for justification see Section I 4.1 of this dossier assessment.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

The risk of bias for the result of the outcome of overall survival is rated as high due to uncertainties in the subsequent therapies administered in the comparator arm (see Section I 3.2).

The risk of bias of the results for the outcome of recurrence is rated as low.

The risk of bias of the results for the outcomes of SAEs and severe AEs as well as for the other specific AEs of pyrexia (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs) and infections and infestations (SOC, AEs) was rated as high in each case. Even though the median treatment durations are similar in the 2 treatment arms (see Table 10), there are clear differences in the reasons for treatment discontinuation. In the intervention arm, 19% of patients discontinued treatment early due to AEs, compared with < 1% in the comparator arm. In contrast, 2% of patients in the intervention arm discontinued treatment due to disease relapse, compared with 22% in the comparator arm. For the mentioned outcomes of the category of side effects, observations are therefore incomplete for different, potentially

informative reasons due to the follow-up observation being linked to the treatment duration and a possible association between outcome and reason for treatment discontinuation.

For the specific AEs that are not serious or severe, another reason for a high risk of bias is the lack of blinding in subjective recording of outcomes. For the outcome of discontinuation due to AEs, this is the sole reason for a high risk of bias.

Summary assessment of the certainty of conclusions

Regardless of the aspects described for the risk of bias, the certainty of conclusions of the study results is limited due to the uncertainties described in Section I 3.2. This is particularly due to the proportion of patients who are no longer included in the present research question. Overall, at most hints, e.g. of an added benefit, can therefore be determined for the results of all outcomes presented.

I 4.3 Results

Table 15 and Table 16 summarize the results of the comparison of atezolizumab with BSC for the adjuvant treatment of adult patients with completely resected NSCLC at high risk of recurrence after platinum-based chemotherapy whose tumours express PD-L1 in ≥ 50% of the tumour cells and who do not have EGFR mutations or ALK-positive NSCLC. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves for the time-to-event analyses of the outcomes in the IMPOwer010 study are shown in I Appendix B of the full dossier assessment. The results on common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, time to event) – RCT, direct comparison: atezolizumab vs. BSC

Study Outcome category Outcome	Atezolizumab N	Atezolizumab Median time to event in months [95% CI] Patients with event n (%)	BSC N	BSC Median time to event in months [95% CI] Patients with event n (%)	Atezolizumab vs. BSC HR [95% CI]; p-value[a]
IMpower010 (data cut-off: 26 January 2024)					
Mortality					
Overall survival	106	NA 22 (20.8)	103	87.1 [72.0; NA] 41 (39.8)	0.47 [0.28; 0.80]; 0.005
Morbidity					
Recurrence					
Recurrence rate	106	– 34 (32.1)	103	– 55 (53.4)	RR: 0.61 [0.44; 0.84]; 0.002[b]
Local recurrence	106	– 4 (3.8[c])	103	– 8 (7.8[c])	–
Regional recurrence	106	– 12 (11.3[c])	103	– 8 (7.8[c])	–
Remote recurrence[d]	106	– 11 (10.4[c])	103	– 28 (27.2[c])	–
New primary lung cancer	106	– 1 (0.9[c])	103	– 3 (2.9[c])	–
Death without recurrence	106	– 6 (5.7)	103	– 8 (7.8)	–
Disease-free survival	106	NA 34 (32.1)	103	42.9 [32.0; NC] 55 (53.4)	0.52 [0.33; 0.80]; 0.003
Health-related quality of life	Outcome not recorded				

a. HR and CI: Cox proportional hazards model, p-value: log-rank test; each stratified by sex, tumour histology, and stage of disease.
b. RR, CI and p-value: log-binomial model; adjusted for sex, tumour histology, and stage of disease.
c. Institute's calculation.
d. Of which 1 patient in the intervention arm versus 11 patients in the comparator arm had CNS recurrence.

BSC: best supportive care; CI: confidence interval; CNS: central nervous system; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial

Table 16: Results (side effects, dichotomous) – RCT, direct comparison: atezolizumab vs. BSC

Study Outcome category Outcome	Atezolizumab N	Atezolizumab Patients with event n (%)	BSC N	BSC Patients with event n (%)	Atezolizumab vs. BSC RR [95% CI]; p-value[a]
IMpower010 (data cut-off: 26 January 2024)					
Side effects					
AEs (supplementary information)	104	99 (95.2)	101	71 (70.3)	–
SAEs	104	16 (15.4)	101	4 (4.0)	3.88 [1.34; 11.22]; 0.006
Severe AEs[b]	104	21 (20.2)	101	11 (10.9)	1.85 [0.94; 3.65]; 0.070
Discontinuation due to AEs	104	20 (19.2)	101	0[c] (0)	39.83 [2.44; 649.84]; < 0.001
Immune-mediated AEs (SAEs, severe AEs)	No suitable data[d]				
Pyrexia (PT, AEs)	104	11 (10.6)	101	0 (0)	22.34 [1.33; 374.20]; < 0.001
Skin and subcutaneous tissue disorders (SOC, AEs)	104	36 (34.6)	101	6 (5.9)	5.83 [2.57; 13.23]; < 0.001
Infections and infestations (SOC, SAEs)	104	7 (6.7)	101	0 (0)	-[e]; 0.008

a. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [22]). In case of zero events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms.
b. Operationalized as CTCAE grade ≥ 3.
c. Presentation taken from Module 4 A of the company. Discontinuation refers to treatment with atezolizumab. In the comparator arm, one patient had discontinued BSC therapy. It is unclear exactly which supportive measure was discontinued.
d. See body of text for reasons.
e. No presentation of effect estimate and CI, as not informative and also discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

As described in Section I 4.2, there are uncertainties that affect the certainty of results. On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of atezolizumab in comparison with BSC. There is a hint of an added benefit of atezolizumab in comparison with watchful waiting for the outcome of overall survival.

Morbidity

Recurrence

For the outcome of recurrence (operationalized as recurrence rate and DFS), a statistically significant difference was found between the treatment arms in favour of atezolizumab in comparison with BSC. There is a hint of an added benefit of atezolizumab in comparison with watchful waiting for this outcome.

Health-related quality of life

No data are available for the outcome of health-related quality of life. There is no hint of an added benefit of atezolizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, a statistically significant difference was found between the treatment arms to the disadvantage of atezolizumab in comparison with BSC. There is a hint of greater harm from atezolizumab in comparison with watchful waiting.

Severe AEs (CTCAE grade ≥ 3)

No statistically significant difference between the treatment arms was found for the outcome of severe AEs (CTCAE grade ≥ 3). There is no hint of greater or lesser harm from atezolizumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, a statistically significant difference was found between the treatment arms to the disadvantage of atezolizumab in comparison with BSC. There is a hint of greater harm from atezolizumab in comparison with watchful waiting.

Specific AEs

Immune-mediated SAEs and immune-mediated severe AEs

No suitable data are available for the outcomes of immune-mediated SAEs and immune-mediated severe AEs. In each case, there is no hint of greater or lesser harm from

atezolizumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Pyrexia (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), infections and infestations (SOC, SAEs)

A statistically significant difference was found between the treatment arms to the disadvantage of atezolizumab in comparison with BSC for each of the outcomes of pyrexia (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), and infections and infestations (SOC, SAEs). In each case, there is a hint of greater harm from atezolizumab in comparison with watchful waiting.

I 4.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered for the present assessment:

- age (< 65 years versus ≥ 65 years)
- sex (male versus female)
- tumour stage (IIA versus IIB versus IIIA)

For the characteristic of tumour stage, the company only presented analyses according to the staging based on the 7th edition of the TNM classification according to UICC/AJCC. As described, the categorization changed partially according to the currently valid 8th edition after the transition. Therefore, no conclusion can be drawn regarding potential effect modifications based on the 8th edition of the TNM classification according to UICC/AJCC; therefore, the subgroup analyses according to the 7th edition are considered as an approximation.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

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

For the outcomes in the side effects category, the Institute performed a test for interaction using the Q-test in relation to the relative risk (RR).

Applying the methods described above, no effect modifications were found.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

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

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 17).

Determination of the outcome category for the outcomes of recurrence and discontinuation due to AEs

It cannot be inferred from the dossier for the outcomes of recurrence and discontinuation due to AEs whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

The outcome of recurrence is considered to be serious/severe. On the one hand, recurrence of the cancer can be life-threatening, and a recurrence shows that the attempt to cure a potentially life-threatening disease with the curative therapy approach has not been successful. On the other hand, the event of death from any cause is a component of the outcome of recurrence.

The outcome of discontinuation due to AEs is allocated to the outcome category of serious/severe side effects because 52% of AEs leading to treatment discontinuation were CTCAE grade ≥ 3 events.

Table 17: Extent of added benefit at outcome level: atezolizumab vs. watchful waiting (multipage table)

Outcome category **Outcome**	**Atezolizumab vs. BSC** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NA vs. 87.1 months HR: 0.47 [0.28; 0.80]; p = 0.005 Probability: "hint"	Outcome category: mortality added benefit, extent: "non-quantifiable"[c]
Morbidity		
Recurrence		
Recurrence rate	32.1% vs. 53.4% RR: 0.61 [0.44; 0.84]; p = 0.002 Probability: "hint"	Outcome category: Serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent "considerable"
Disease-free survival	NA vs. 42.9 months HR: 0.52 [0.33; 0.80]; p = 0.003 Probability: "hint"	
Outcomes with shortened observation period		
Health-related quality of life		
Outcome not recorded		
Side effects		
SAEs	15.4% vs. 4.0% RR: 3.88 [1.34; 11.22]; RR: 0.26 [0.09; 0.74][d]; p = 0.006 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"
Severe AEs	20.2% vs. 10.9% RR: 1.85 [0.94; 3.65]; RR: 0.54 [0.27; 1.06][d]; p = 0.070 Probability: "hint"	Greater/lesser harm not proven
Discontinuation due to AEs[e]	19.2% vs. 0% RR: 39.83 [2.44; 649.84]; RR: 0.03 [0.00; 0.41][d]; p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"

Table 17: Extent of added benefit at outcome level: atezolizumab vs. watchful waiting (multipage table)

Outcome category **Outcome**	**Atezolizumab vs. BSC** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Immune-mediated SAEs and severe AEs	No suitable data	Greater/lesser harm not proven
Pyrexia (AEs)	10.6% vs. 0% RR: 22.34 [1.33; 374.20]; RR: 0.04 [0.00; 0.75][d]; p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: "considerable"
Skin and subcutaneous tissue disorders (AEs)	34.6% vs. 5.9% RR: 5.83 [2.57; 13.23]; RR: 0.17 [0.08; 0.39][d]; p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: "considerable"
Infections and infestations (SAEs)	6.7% vs. 0% RR: –[f]; p = 0.008 Probability: "hint"	Outcome category: serious/severe side effects Greater harm, extent: "non-quantifiable"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. See Sections I 4.1 and I 4.2 for reasons.
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.
e. Allocated to the outcome category of serious/severe side effects because 52.4% of AEs leading to treatment discontinuation were CTCAE grade ≥ 3 events.
f. No presentation of effect estimate and CI, as not informative and also discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of the confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; NA: not achieved; RR: relative risk; SAE: serious adverse event

I 5.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of atezolizumab in comparison with watchful waiting

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Mortality ▪ Overall survival: hint of an added benefit – extent: "non-quantifiable"	–
Morbidity Serious/severe symptoms/late complications ▪ Recurrence: hint of an added benefit – extent: "considerable"	–
Outcomes with shortened observation period	
–	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: "major" ▪ infections and infestations (SAEs): hint of greater harm – extent: "non-quantifiable" ▪ Discontinuation due to AEs: hint of greater harm – extent "major"
–	Non-serious/non-severe side effects ▪ Pyrexia (AEs): hint of greater harm – extent "considerable" ▪ Skin and subcutaneous tissue disorders (AEs): hint of greater harm – extent: "considerable"
Outcomes on symptoms and health-related quality of life were not recorded in the relevant study. No suitable data are available on the outcomes of immune-mediated SAEs and immune-mediated severe AEs.	
AE: adverse event; SAE: serious adverse event	

Overall, there are both positive and negative effects of atezolizumab in comparison with watchful waiting.

On the side of positive effects, there are hints of a non-quantifiable added benefit for the outcome of overall survival, and of a considerable added benefit for the outcome of recurrence.

On the other hand, there are hints of greater harm with different, in some cases major extent for some outcomes in the side effects category. The negative effects in the side effects do not completely call into question the positive effects in the outcomes of overall survival and recurrence. No conclusion can be drawn on the patients' symptoms and health-related quality of life, as these outcomes were not recorded in the IMpower010 study. In addition, suitable analyses of immune-mediated SAEs and immune-mediated severe AEs are lacking.

In summary, there is a hint of a minor added benefit of atezolizumab in comparison with the ACT watchful waiting for the adjuvant treatment of patients with completely resected NSCLC

at high risk of recurrence after platinum-based chemotherapy whose tumours express PD-L1 in ≥ 50% of the tumour cells and who do not have EGFR mutations or ALK-positive NSCLC.

The result of the assessment of the added benefit of atezolizumab in comparison with the ACT is summarized in Table 19.

Table 19: Atezolizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with completely resected NSCLC at high risk of recurrence after platinum-based chemotherapy whose tumours express PD-L1 in ≥ 50% of the tumour cells and who do not have EGFR mutations or ALK-positive NSCLC; adjuvant treatment	Watchful waiting	Hint of minor added benefit
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1		

The assessment described above deviates from that by the company, which derived an indication of major added benefit.

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

I 6 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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