IQWiG Reports – Commission No. A22-67

# Atezolizumab (NSCLC, adjuvant) –

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

## Extract

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Atezolizumab (NSCLC, adjuvant) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 October 2022). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

**Patient and family involvement**

No feedback of persons concerned or patient organizations was received within the framework of the present dossier assessment..

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# 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 |
| AEOSI | adverse events of special interest |
| AJCC | American Joint Committee on Cancer |
| ALK | anaplastic lymphoma kinase |
| BSC | best supportive care |
| CT | computed tomography |
| DFS | disease-free survival |
| ECOG-PS | Eastern Cooperative Oncology Group Performance Status |
| EGFR | epidermal growth factor receptor |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| NSCLC | non-small cell lung cancer |
| PD-L1 | programmed cell death ligand 1 |
| PT | Preferred Term |
| RCT | randomized controlled trial |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SOC | System Organ Class |
| SPC | Summary of Product Characteristics |
| TNM | classification of malignant tumours |
| 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 5 July 2022.

### Research question

Aim of the present report is the assessment of the added benefit of atezolizumab in comparison with watchful waiting as appropriate comparator therapy (ACT) in the adjuvant treatment of adult patients with non-small cell lung cancer (NSCLC) after complete resection and platinum-based chemotherapy at high risk of recurrence. Patients should have programmed cell death ligand 1 (PD-L1) expression in ≥ 50% of tumour cells and not have epidermal growth factor receptor (EGFR)-mutated 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[b] |

a. Presented is the respective ACT specified by the G-BA.
b. At the time of application of the therapy to be assessed, the patients are to be considered disease-free. For patients with completely resected NSCLC, there are no approvals or recommendations for further adjuvant drug or non-drug treatment after adjuvant cisplatin-based chemotherapy (and in individual cases, but not regularly, subsequent radiotherapy). Therefore, the G-BA considers watchful waiting as the adequate ACT.

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 company followed the G-BA's specification of the ACT.

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) are used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

### Results

Concurring with the company, the RCT IMpower010 was identified and classified as potentially relevant. However, the data presented by the company are not suitable for deriving

statements on the added benefit of atezolizumab compared to the ACT, as overall there are no usable data for a balancing of the benefits and harms. In the following, the study IMpower010 as well as the presented analyses are described and the non-suitability is justified.

***Evidence presented by the company – Impower010 study***

Impower110 is an ongoing, open-label, randomized multicentre RCT 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 (see following section). Patients had to have a good general condition corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 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 planned in the IMpower010 study.

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

*Data cut-offs*

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

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

The company used the 2nd data cut-off for the benefit assessment for all outcomes - with the exception of DFS.

*Subpopulation presented by the company*

In Module 4 A of the dossier, the company presents analyses for the subpopulation of patients in stages II to IIIA whose tumours had PD-L1 expression in ≥ 50% of the 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. Points of criticism on the patient population presented by the company can be found below.

*Implementation of the ACT*

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

***Results presented on outcomes of mortality and morbidity not suitable for the benefit assessment***

In Module 4 A, the company used analyses on the outcomes of mortality (overall survival), morbidity (DFS) and side effects (adverse events [AEs] for the benefit assessment. However, the results of the outcome "overall survival" cannot be interpreted in the present data situation and the analyses on DFS are incomplete. This is justified below.

*Results on overall survival not interpretable due to inadequate subsequent therapies*

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 necessary, especially in the adjuvant therapy situation.

However, the subsequent systemic therapies administered in the comparator arm of the IMpower010 study do not adequately reflect the current standard of therapy after the occurrence of a relapse: At the first data cut-off (January 2021), a total of 43 patients in the comparator arm of the subpopulation submitted by the company experienced a recurrence. Only 25 (58%) patients with recurrence in the comparator arm received subsequent systemic therapy, and a maximum of 20 (47%) patients received an immune checkpoint inhibitor. At least 23 (53%) of the patients with recurrence thus received no adequate subsequent therapy. It is not clear from the information in Module 4 A of the dossier why not nearly all patients were treated with an immune checkpoint inhibitor in accordance with the guidelines after the occurrence of a relapse, or for what reasons 18 patients with recurrence received no subsequent systemic therapy at all. In addition, it remains unclear whether those patients who were treated with an immune checkpoint inhibitor also received it in accordance with the guidelines as part of the first subsequent therapy. For the 2nd data cut-off (April 2022), the company did not provide any

information on the number of patients with recurrence (see also below); an exact assessment of the subsequent therapies for the 2nd data cut-off is therefore not possible. Compared to the 1st data cut-off, however, only 3 more patients in the comparator arm received subsequent systemic therapy, so that there is still a clear discrepancy between patients with recurrence and patients with (adequate) subsequent systemic therapy also at the 2nd data cut-off (approx. 15 months later). Data on subsequent non-drug therapies for the subpopulation presented by the company are not available.

On the basis of the available data, it must therefore be assumed 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 is associated with a clear survival advantage in advanced or metastatic disease. 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 relapse, as has been the case up to now. Thus, treatment with an immune checkpoint inhibitor is also preferred in the adjuvant treatment situation in the IMpower010 study presented by the company. However, due to the insufficient treatment with immune checkpoint inhibitors after the occurrence of a relapse in the comparator arm of the IMpower010 study, this research question cannot be answered. It is unclear whether the effect on overall survival observed in the subpopulation presented would continue to exist with adequate use of immune checkpoint inhibitors in subsequent therapy. Therefore, the results on overall survival in the IMpower010 study cannot be interpreted.

*No usable data on DSF and on the recurrence rate*

The analyses on the outcomes “DFS” and “recurrence rate” cannot be used for the benefit assessment, as the company only presented results for the 1st data cut-off of January 2021. It is not appropriate that the company presents no analyses on DFS and recurrence rate for the current data cut-off of April 2022 with a follow-up observation period that is approx. 15 months longer. The analyses prepared on the basis of the 1st data cut-off and presented by the company only cover about 70% of the available observation period of the Impower010 study. With the longer observation period for the 2nd data cut-off, data with a higher information content are thus available for the outcomes of DFS and recurrence rate. Accordingly, analyses on the outcomes “DFS” and “recurrence rate” at the 2nd data cut-off are necessary for the benefit assessment.

***Conclusion***

In summary, the results on the outcome “overall survival” cannot be interpreted due to the insufficient administration of immune checkpoint inhibitors as part of the subsequent therapy in the comparator arm. Moreover, there are no usable results on patient-relevant outcomes of the category “morbidity” (DFS, recurrence rate). Outcomes on symptoms and health-related quality of life were not recorded in the IMpower010 study. As usable results on the benefit

outcomes are missing, a balancing of benefit and harm is not possible on the basis of the available data. Therefore, the analyses on the IMpower010 study presented by the company are unsuitable for the benefit assessment.

***Further points of criticism***

Irrespective of the fact that the analyses of the IMpower010 study submitted by the company are not suitable for the benefit assessment for the reasons described above, there are the following further relevant points of criticism on the data submitted by the company:

- In the subpopulation of the IMpower010 study presented by the company, the time interval between tumour resection and the start of adjuvant platinum-based chemotherapy was > 60 days for approx. 35% of the patients. However, for an interval of > 60 days, there is no evidence for the efficacy of adjuvant chemotherapy from randomized prospective controlled comparative studies. It is unclear whether and to what extent adjuvant chemotherapy is started despite a time interval of > 60 days after surgery also in the German health care context.
- There is uncertainty as to whether at least 80% of the patients in the subpopulation formed by the company are covered by the present research question:
  - 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. The company did not present information on the use of CT and MRI scans of the cranium.
  - The inclusion of the patients in the IMpower010 study was based on the 7th edition of the classification of malignant tumours (TNM) classification according to UICC/AJCC. In its dossier, the company transfers the staging to the currently valid 8th edition of the TNM classification, which leads to shifts in the tumour stage for some of the tumours. Due to the shifts in the staging, a maximum of 19.1% of the patients can no longer be assigned to stages II - IIIA and are therefore no longer included in the present research question.
  - According to the SPC, the use of atezolizumab in adjuvant treatment is limited to patients who do not have EGFR-mutated or ALK-positive NSCLC. However, the EGFR and ALK mutation status is unknown in about 45% of the patients in the subpopulation presented. The presence of an EGFR or ALK mutation can be assumed for some of these patients, who would thus not be included in the present research question.

Moreover, there is the following further point of criticism:

- The company did not present a summary analysis of events for immune-related AEs (AEs, serious AEs, severe AEs). Instead, in Module 4 A, it only presents results for individual categories of immune-related AEs within the framework of the analyses on the specific AEs of special interest (AEOSI). The analysis presented by the company is therefore not suitable to provide a comprehensive reflection of the immune-related AEs.

It should also be noted that the data on AEs provided by the company are inadequately prepared. In Appendix 4 G of the dossier, the company presents results on all AEs according to System Organ Class (SOC) and Preferred Term (PT) without, however, taking into account the frequency thresholds according to the dossier template.

**Results on added benefit**

Since no usable data are available for the benefit assessment, this resulted in no hint of an added benefit of atezolizumab in comparison with the ACT; an added benefit is therefore not proven.

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

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

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[b] | Added benefit not proven |

a. Presented is the respective ACT specified by the G-BA.
b. At the time of application of the therapy to be assessed, the patients are to be considered disease-free. For patients with completely resected NSCLC, there are no approvals or recommendations for further adjuvant drug or non-drug treatment after adjuvant cisplatin-based chemotherapy (and in individual cases, but not regularly, subsequent radiotherapy). Therefore, the G-BA considers watchful waiting as the adequate ACT.

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 G-BA decides on the added benefit.

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

## I 2 **Research question**

Aim of the present report is the assessment of the added benefit of atezolizumab in comparison with watchful waiting as ACT in the adjuvant treatment of adult patients with NSCLC after complete resection and platinum-based chemotherapy at high risk of recurrence. Patients should have PD-L1 expression in ≥ 50% of tumour cells and not have EGFR-mutated 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[b] |
| a. Presented is the respective ACT specified by the G-BA.<br>b. At the time of application of the therapy to be assessed, the patients are to be considered disease-free. For patients with completely resected NSCLC, there are no approvals or recommendations for further adjuvant drug or non-drug treatment after adjuvant cisplatin-based chemotherapy (and in individual cases, but not regularly, subsequent radiotherapy). Therefore, the G-BA considers watchful waiting as the adequate ACT.<br>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 company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used for the derivation of 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 list on atezolizumab (status: 2 May 2022)
- bibliographical literature search on atezolizumab (last search on 2 May 2022)
- search in trial registries/trial results databases for studies on atezolizumab (last search on 2 May 2022)
- search on the G-BA website for atezolizumab (last search on 2 May 2022)

To check the completeness of the study pool:

- search in trial registries for studies on atezolizumab (last search on 20 July 2022); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant studies.

The company identified the RCT IMpower010 [3-8] and used it for its assessment.

Concurring with the company, the RCT IMpower010 was identified and classified as potentially relevant. However, the data presented by the company are not suitable for deriving statements on the added benefit of atezolizumab compared to the ACT, as overall there are no usable data for a balancing of the benefits and harms. In the following, the study IMpower010 as well as the presented analyses are described and the non-suitability is justified.

### Evidence provided by the company

#### *Design of the IMpower010 study*

Impower110 is an ongoing, open-label, randomized multicentre RCT 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/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 to 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 vs. female), histology (squamous vs. non-squamous), disease stage (IB vs. II vs. 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 vs. TC0/1 and IC2/3 vs. TC0/1 and IC0/1).

Treatment with atezolizumab in the intervention arm was in compliance with the specifications of the SPC [9]. A switch of the patients from the comparator arm to treatment with atezolizumab was not planned in the IMpower010 study.

Primary outcome of the IMpower010 study was DFS. Further secondary outcomes were outcomes of the categories "mortality", "morbidity" and "side effects".

*Data cut-offs*

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

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

The company used the 2nd data cut-off for the benefit assessment for all outcomes - with the exception of DFS.

*Subpopulation presented by the company*

In Module 4 A of the dossier, the company presents analyses for the subpopulation of patients in stages II to IIIA whose tumours had PD-L1 expression in ≥ 50% of the 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 ACT. The IMpower010 study used BSC as comparator therapy. The study was not designed for a comparison with watchful waiting, but is basically nonetheless suitable for such a comparison. The examinations carried out in the study do not fully correspond to the recommendations of the currently valid guidelines [10,11]; however, the examination regimen in the IMpower010 study is in principle considered to be a sufficient approximation to the ACT of watchful waiting.

Further details on the characteristics of the IMpower010 study, the interventions used in the study, and the patients included can be found in I Appendix B of the full dossier assessment. Points of criticism on the patient population presented by the company can be found below.

***Results presented on outcomes of mortality and morbidity not suitable for the benefit assessment***

In Module 4 A, the company used analyses on the outcomes of mortality (overall survival), morbidity (DFS) and side effects (AEs for the benefit assessment. However, the results of the outcome "overall survival" cannot be interpreted in the present data situation and the analyses on DFS are incomplete. This is justified below.

*Results on overall survival not interpretable due to inadequate subsequent therapies*

An observed effect in the outcome "overall survival" is not only influenced by the initial study treatment, but also by the subsequent antineoplastic therapies used after disease progression or recurrence [12-14]. 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.

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 and PD-L1 expression ≥ 50% should receive systemic therapy with an immune checkpoint inhibitor or a combination of immune checkpoint inhibitor and chemotherapy in the first-line setting [10,11]. These recommendations are based on clear advantages in overall survival with immune checkpoint inhibitors compared to platinum-based chemotherapy [15-18]. According to these findings and the recommendations of the guidelines, it can therefore be assumed that subsequent therapy using an immune checkpoint inhibitor would have been indicated for almost all patients with recurrence in the comparator arm in the subpopulation of the IMpower010 study presented by the company.

However, the subsequent systemic therapies administered in the comparator arm of the IMpower010 study do not adequately reflect the current treatment standard after the occurrence of a relapse: At the first data cut-off (January 2021), a total of 43 patients in the comparator arm

of the subpopulation submitted by the company had a recurrence (see Table 9 of the full dossier assessment). Only 25 (58%) patients with recurrence in the comparator arm received subsequent systemic therapy, and a maximum of 20 (47%) patients received an immune checkpoint inhibitor. At least 23 (53%) of the patients with recurrence thus received no adequate subsequent therapy. It is not clear from the information in Module 4 A of the dossier why not nearly all patients were treated with an immune checkpoint inhibitor in accordance with the guidelines after the occurrence of a relapse, or for what reasons 18 patients with recurrence received no subsequent systemic therapy at all. In addition, it remains unclear whether those patients who were treated with an immune checkpoint inhibitor also received it in accordance with the guidelines as part of the first subsequent therapy. For the 2nd data cut-off (April 2022), the company did not provide any information on the number of patients with recurrence (see also below); an exact assessment of the subsequent therapies for the 2nd data cut-off is therefore not possible. Compared to the 1st data cut-off, however, only 3 more patients in the comparator arm received subsequent systemic therapy (see Table 9 of the full dossier assessment), so that there is still a clear discrepancy between patients with recurrence and patients with (adequate) subsequent systemic therapy also at the 2nd data cut-off (approx. 15 months later). Data on subsequent non-drug therapies for the subpopulation presented by the company are not available.

On the basis of the available data, it must therefore be assumed 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 is associated with a clear survival advantage in advanced or metastatic disease. 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 relapse, as has been the case up to now [19]. Thus, treatment with an immune checkpoint inhibitor is also preferred in the adjuvant treatment situation in the IMpower010 study presented by the company. However, due to the insufficient treatment with immune checkpoint inhibitors after the occurrence of a relapse in the comparator arm of the IMpower010 study, this research question cannot be answered. It is unclear whether the effect on overall survival observed in the subpopulation presented would continue to exist with adequate use of immune checkpoint inhibitors in subsequent therapy. The results on overall survival in the IMpower010 study were therefore not interpretable.

*No usable data on DSF and on the recurrence rate*

The analyses on the outcomes “DFS” and “recurrence rate” cannot be used for the benefit assessment, as the company only presented results for the 1st data cut-off of January 2021. According to the study protocol, this data cut-off was planned as the 1st interim analysis of the outcome “DFS” after the occurrence of 190 DFS events in stage II to IIIA patients with PD-L1 expression in ≥ 1% of tumour cells. The company therefore considers the 1st data cut-off for the DFS to be relevant to the assessment.

The company's approach is not appropriate. The dossier template generally specifies for complete analyses of all recorded patient-relevant outcomes to be carried out and presented for the data cut-offs submitted by the company, even in cases where a data cut-off was originally planned for the analysis of only some of the outcomes [20]. It is not appropriate that the company presents no analyses on DFS and recurrence rate for the current data cut-off of April 2022 with a follow-up observation period that is approx. 15 months longer. The analyses prepared on the basis of the 1st data cut-off and presented by the company only cover about 70% of the available observation period of the Impower010 study. With the longer observation period for the 2nd data cut-off, data with a higher information content are thus available for the outcomes of DFS and recurrence rate. Accordingly, analyses on the outcomes "DFS" and "recurrence rate" at the 2nd data cut-off are necessary for the benefit assessment.

In addition, it should be noted that according to the study protocol, in addition to the assessment of DFS by the investigators, a blinded independent central review (BICR) of DFS should also be performed based on the radiographic as well as other clinical data. However, the analyses of the BICR are incomplete, as only 53% of the patients in the subpopulation presented by the company were included in the analysis.

**Conclusion**

In summary, the results on the outcome "overall survival" cannot be interpreted due to the insufficient administration of immune checkpoint inhibitors as part of the subsequent therapy in the comparator arm. Moreover, there are no usable results on patient-relevant outcomes of the category "morbidity" (DFS, recurrence rate). Outcomes on symptoms and health-related quality of life were not recorded in the IMpower010 study. As usable results on the benefit outcomes are missing, a balancing of benefit and harm is not possible on the basis of the available data. Therefore, the analyses on the IMpower010 study presented by the company are unsuitable for the benefit assessment.

**Further points of criticism**

Irrespective of the fact that the analyses of the IMpower010 study submitted by the company are not suitable for the benefit assessment for the reasons described above, there are the following further relevant points of criticism on the data submitted by the company:

- In the subpopulation of the IMpower010 study presented by the company, the time interval between tumour resection and the start of adjuvant platinum-based chemotherapy was > 60 days for approx. 35% of the patients. However, for an interval of > 60 days, there is no evidence for the efficacy of adjuvant chemotherapy from randomized prospective controlled comparative studies. The guidelines therefore recommend starting adjuvant chemotherapy within 60 days of tumour resection [10,11]. The company addresses the recommendation of the guidelines in Module 3 A and refers to the results of a retrospective analysis of patient data by the National Cancer Database in the USA, which show no influence of a delayed start of adjuvant chemotherapy (i.e. a start after more than 8 weeks) on survival [21]. However, based on the available data, it remains

unclear for the IMPower010 study whether a delayed start of adjuvant chemotherapy (> 60 days) has an influence on the observed effects. Subgroup analyses (≤ 60 days vs. > 60 days) had not been planned and were not presented by the company in Module 4. It is unclear whether and to what extent adjuvant chemotherapy is started despite a time interval of > 60 days after surgery also in the German health care context.

- There is uncertainty as to whether at least 80% of the patients in the subpopulation formed by the company are covered by the present research question:
  - To exclude cerebral metastasis, both a MRI scan and a CT scan were accepted in the IMpower010 study. According to the guideline recommendation, however, a CT scan to exclude brain metastases should only be performed if there is a contraindication to an MRI scan [10]. 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.
  - The inclusion of the patients in the IMpower010 study was based on the 7th edition of the TNM classification according to UICC/AJCC. In its dossier, the company transfers the staging to the currently valid 8th edition of the TNM classification, which leads to shifts in the tumour stage for some of the tumours. However, according to the company, not all tumour descriptions could be exactly reassigned. The information provided by the company in the dossier shows that, due to the shifts in the staging, some patients in the presented subpopulation can no longer be assigned to stages II - IIIA, for which an indication for adjuvant chemotherapy exists according to the guideline recommendation [10,11]. This affects at most 19.1% of the patients, who are therefore no longer included in the present research question. However, the company did not exclude these patients from the analyses and did not present any corresponding sensitivity analyses.
  - According to the SPC, the use of atezolizumab in adjuvant treatment is limited to patients who do not have EGFR-mutated or ALK-positive NSCLC [9]. However, the EGFR and ALK mutation status is unknown in about 45% of the patients in the subpopulation presented. For some of these patients, the presence of an EGFR or ALK mutation can be assumed. Accordingly, these patients are not covered by the therapeutic indication, in some cases, adjuvant therapies are already available for these patients (osimertinib for patients with EGFR-mutated NSCLC [exon 19 deletion or exon 21 L858R substitution mutation]) [11].

Moreover, there is the following further point of criticism:

- The company did not present a summary analysis of events for immune-related AEs (AEs, serious AEs, severe AEs). Instead, in Module 4 A, it only presents results for individual categories of immune-related AEs within the framework of the analyses on the

specific AEOSI. The analysis presented by the company is therefore not suitable to provide a comprehensive reflection of the immune-related AEs.

It should also be noted that the data on AEs provided by the company are inadequately prepared. According to the dossier template, in addition to the overall AE rates, results on all AEs (operationalized as SOCs and PTs according to the Medical Dictionary for Regulatory Activities [MedDRA]) are to be presented if they exceed certain frequency thresholds [20]. In Appendix 4 G of the dossier, the company presents results on all AEs according to SOC and PT without, however, taking into account the frequency thresholds according to the dossier template.

## I 4 **Results on added benefit**

No suitable data are available for the assessment of the added benefit of atezolizumab compared with the ACT for the adjuvant treatment of adult patients with NSCLC after complete resection and platinum-based chemotherapy with a high risk of recurrence and whose tumours have PD-L1 expression in ≥ 50% of the tumour cells and do not have EGFR-mutated or ALK-positive NSCLC. Hence, there was no hint of an added benefit of atezolizumab in comparison with the ACT; an added benefit is therefore not proven.

## I 5 **Probability and extent of added benefit**

The result of the assessment of the added benefit of atezolizumab in comparison with the ACT is summarized in Table 5.

Table 5: 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[b] | Added benefit not proven |

a. Presented is the respective ACT specified by the G-BA.
b. At the time of application of the therapy to be assessed, the patients are to be considered disease-free. For patients with completely resected NSCLC, there are no approvals or recommendations for further adjuvant drug or non-drug treatment after adjuvant cisplatin-based chemotherapy (and in individual cases, but not regularly, subsequent radiotherapy). Therefore, the G-BA considers watchful waiting as the adequate ACT.

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 of the company, which derived an indication of major added benefit based on the results of the IMpower010 study.

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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